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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K

A2

(11) International Publication Number: WO 94/20062

(43) International Publication Date: 15 September 1994 (15.09.94)

(21) International Application Number: PCT/US94/02283

(22) International Filing Date: 2 March 1994 (02.03.94)

(30) Priority Data:
08/025,846 3 March 1993 (03.03.93) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/025,846 (CIP)
Filed on 3 March 1993 (03.03.93)

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(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: BALANOIDS

(57) Abstract

A novel class of therapeutic compounds, denominated Balanoids, is disclosed. Balanoids have protein kinase C inhibitory activity and selectivity among the isoforms of protein kinase C. Balanoids are useful for treatment of diseases related to protein kinase C in animals, especially humans and is especially indicated for treatment of inflammatory diseases.

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BALANOIDS

FIELD OF THE INVENTION

The present invention relates to the field of treatments for inflammatory, cardiovascular, metabolic, nervous system, viral infectious, neoplastic and other diseases. The invention provides compounds which can inhibit protein kinase C enzymes. More particularly, the present invention relates to novel compounds which are referred to herein as "balanoids".

BACKGROUND OF THE INVENTION

Protein kinase C (PKC) is a family of calcium- and phospholipid-dependent serine/threonine-specific protein kinases which play an important role in cellular growth control, regulation, and differentiation. Protein kinase C is activated by diacylglycerol (DAG), a neutral lipid, and when activated will transfer the γ-phosphate of MgATP to a serine or threonine residue on a substrate protein. The mechanisms of protein kinase C action have been described in U.S. Patent 4,816,450 issued March 28, 1989 to Bell *et al.*, which is incorporated herein by reference.

The activation of protein kinase C has been implicated in several human disease processes, including cancer tumors, inflammation and reperfusion injury. Accordingly, protein kinase C is a target for therapeutic agents useful in treating these conditions.

Cancer is a disease characterized in part by uncontrolled cell growth. Protein kinase C is directly involved in cellular growth control and is believed to be involved in tumor formation. Protein kinase C is fundamental

to the processes involved in tumorigenicity, since it is the major high-affinity receptor for endogenous cellular DAGs as well as for several classes of tumor promoters. These tumor promoters also stimulate protein kinase C catalysis. Castagna *et al.*, (1982) *J. Biol. Chem.* 257:7847, reported direct activation of protein kinase C by tumor promoting phorbol esters.

Protein kinase C is the major, if not exclusive, intracellular receptor of phorbol esters, which are very potent tumor promoters. Phorbol esters and other tumor promoters bind to and activate protein kinase C. Since DAG and phorbol esters interact at the same site, DAGs have been suggested to be the "endogenous phorbol esters", analogous to the opiate receptor where the conservation of a high affinity receptor implied the existence of an endogenous analogue. DAG has been shown to increase the affinity of protein kinase C for Ca^{+2} and phospholipid and thus activates protein kinase C at cellular levels of these essential cofactors. Extracellular signals including hormones, growth factors, and neurotransmitters are known to stimulate phosphatidylinositol turnover resulting in the generation of IP_3 and DAG.

Structures of 40 distinct oncogenes of viral and cellular origin have revealed that oncogenes encode altered forms of normal cellular proteins. Several of the gene products appear related to growth factors or other elements involved in transmembrane signalling. These oncogene products appear to function by altering the level of critical second messengers. Cells transformed with the oncogenes *ras*, *sis*, *erbB*, *abl*, and *src* have been shown to contain elevated levels of DAG which is then believed to activate protein kinase C. Studies on *ras* transformed cells have shown protein kinase C activation to be concomitant with elevation of DAG.

Phorbol esters, such as phorbol myristate acetate (PMA), have complex effects on cells including effects on membrane function, mitogenesis, differentiation, and gene expression. Synthetic DAGs mimic many of the effects of PMA *in vitro* and inhibitors of protein kinase C have been shown to

block PMA-induced effects on cells. Thus, protein kinase C may mediate the actions of certain oncogenes, such as *ras*, which cause intracellular increases in DAG and concomitant increases in protein kinase C. In addition, activation of protein kinase C leads to the expression of *c-myc*, *c-fos*, *c-cis*, *c-fms*, nuclear protooncogenes which are important in cell transformation. Overexpression of protein kinase C in NIH 3T3 cells causes altered growth regulation and enhanced tumorigenicity, and in rat fibroblasts leads to anchorage-independent growth in soft agar. Overexpression of protein kinase C in these cells resulted in tumor formation in animals receiving transplanted cells.

Several studies have shown increased expression of protein kinase C in certain tumor types such as breast and lung carcinomas. Activated protein kinase C has also been detected in human colon carcinomas although increased expression at the gene level was not seen. Topoisomerases are directly modulated by protein kinase C as substrates for the enzyme.

Protein kinase C inhibitors have been reported to potentiate the antitumor activity of chemotherapeutic agents such as cis-platin both *in vitro* and *in vivo* (Grunicke, *et al.* (1989) *Adv. Enzyme Regul.* **28**:201; and German Offenlegungsschrift DE 3827974). In addition, it has been suggested that protein kinase C would be a potential target for therapeutic design because of its central role in cell growth (Tritton, T.R. and J.A. Hickman, (1990) *Cancer Cells* **2**:5-102). German Offenlegungsschrift DE 3827974 A1 discloses therapeutic preparations comprising a protein kinase C inhibitor in combination with a lipid, a lipid analogue, a cytostatic agent or phospholipase inhibitor which are useful for cancer therapy.

Inflammation and reperfusion injury, particularly pertaining to cardiac injury, are common conditions for which there exists no definitive treatment despite extensive research. Appropriate treatments for these conditions are needed.

Protein kinase C inhibitors have been demonstrated to block platelet aggregation and release of neutrophil activating

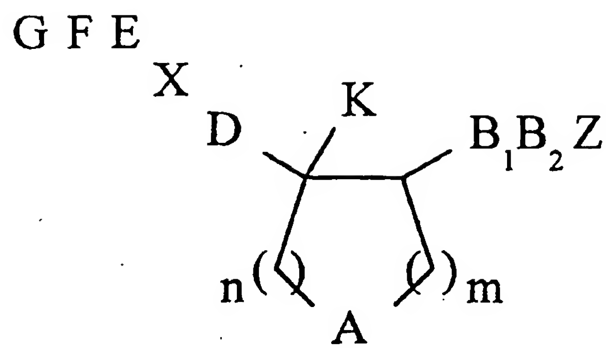
agents such as platelet activating factor (PAF) (Schachtele, *et al.* (1988) *Biochem. Biophy. Res. Commun.* 151:542; Hannun, *et al.* (1987) *J. Biol. Chem.* 262:13620; Yamada, *et al.* (1988) *Biochem. Pharmacol.* 37:1161). Protein kinase C inhibitors have also been shown to inhibit neutrophil activation, and chemotactic migration (McIntyre, *et al.* (1987) *J. Biol Chem.* 262:15730; Lambreth, *et al.* (1988) *J. Biol. Chem.* 263:3818; Pittet, *et al.* (1987) *J. Biol. Chem.* 262:10072; and Gaudry, *et al.* (1988) *Immunology* 63:715), as well as neutrophil degranulation and release of proteolytic enzymes and reactive oxygen intermediates (Wilson, *et al.* (1986) *J. Biol. Chem.* 261:12616; Fujita *et al.* (1986) *Biochem. Pharmacol.* 35:4555; Berkow, *et al.* (1987) *J. Leukoc. Biol.* 41:441; Salzer, *et al.* (1987) *Biochem. Biophys. Res. Commun.* 148:747; Kramer, *et al.* (1989) *J. Biol. Chem.* 262:5876; and Dewald, *et al.* (1989) *Biochem. J.* 264:879).

Thus, inhibitors of protein kinase C have the capability of blocking all three of the most significant mechanisms of pathogenesis associated with myocardial reperfusion injury. Protein kinase C is, accordingly, a drug target for therapeutic agents. Additionally, the inhibitory effect of protein kinase C inhibitors on keratinocytes, and on the oxidative burst in neutrophils, provides an anti-inflammatory effect.

Groth, T., *et al.*, *Proc. Adabori Conf: 3rd Ger.-Jap. Symp. Pept. Chem.*, E. Wuensch, ed., 91 (1989) disclose ophiocordin, an antibiotic with antifungal activity having certain structural similarities to certain compounds of the invention.

SUMMARY OF THE INVENTION

The present invention relates to a novel class of compounds referred to herein as balanoids. Compounds according to the present invention have the following formula:



wherein:

A is: CH_2, NR^1, S, SO_2 or O;

B_1 is: NR^2, O or CH_2;

B_2 is: CO, CS, or SO_2;

Z is: R^4, aryl, heteroaryl, substituted aryl or substituted heteroaryl;

D is: NR^3, O or CH_2;

E is: R^5, aryl, heteroaryl, substituted aryl or substituted heteroaryl;

F is: CO, CS, $CH(OR^6)$, CH_2, O, S or NR^6;

G is: R^7, aryl, heteroaryl, substituted aryl, substituted heteroaryl or substituted cycloalkyl;

K is: hydrogen or lower alkyl;

X is: CO, CS, CH_2, CNR^8 or CCR^9R^{10};

R^1, R^2, R^3, R^4, R^6, R^7, R^8, R^9 and R^{10} are, independently, hydrogen, lower alkyl, aryl or JR^{11};

R^5 is: lower alkyl or aryl;

J is: CO, $C{=}NR^{12}$, SO_2 or P(O)O alkyl;

R^{11} is: hydrogen, lower alkyl, aryl, alkamino, arylamino, aryloxy or alkoxy;

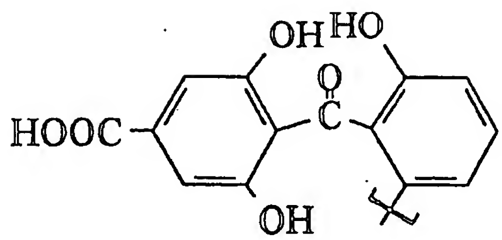
R^{12} is: straight or branched alkyl, aryl;

m is: 1-4;

n is: 1-4; and

m plus n is up to 5;

providing that if m is 3, A is NH, B_1 is O, B_2 is CO, Z is p-hydroxyphenyl, D is NH, X is CO, and E, F, and G, tak n together, are



then n is not 1.

Additionally, the present invention relates to pharmaceutically acceptable salts of the above compounds and to formulations comprising the above compounds in pharmaceutically acceptable carriers. Prodrugs such as carbonates and esters of phenolic functional groups and other species metabolizable into compounds of the invention are also considered to be within the scope of the present invention.

The present invention relates to a method of inhibiting protein kinase C activity which comprises contacting protein kinase C with an inhibitory amount of a balanoid of the invention.

The present invention also relates to methods of treating an animal, preferably a mammal, that is suffering from a PKC-related disease, especially an inflammatory, cardiovascular and/or neoplastic diseases by administering an effective amount of a balanoid to the animal.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

This invention is directed to a family of novel compounds denominated "balanoids". Members of the family have been found to exhibit the ability to inhibit enzymes of the family of enzymes known as protein kinase C enzymes. Selectivity in inhibitors among the isoforms of protein kinase C (PKC) has been shown for balanoids and it is believed that balanoids will be useful in the treatment of disease linked to PKC enzymes.

Methods for preparing balanoids together with synthetic intermediates, are further objects of the invention as are methods for testing for PKC-linked diseases.

The present invention relates to balanoids, and their pharmaceutically acceptable salts and formulations. Compounds according to the present invention have been shown to inhibit protein kinase C. PKC inhibitors are known to be useful in the treatment of cancer, inflammatory and reperfusion injury through their antiproliferative and anti-inflammatory activities in human neutrophils, human keratinocytes, and human tumor cells.

The present invention relates to methods of inhibiting protein kinase C activity which comprises contacting said protein kinase C with an effective amount of a balanoid or a pharmaceutically acceptable salt thereof. Protein kinase C inhibitors are useful as anti-inflammatory, antitumor, and reperfusion injury agents through their antiproliferative and anti-inflammatory activities in human neutrophils, human keratinocytes, and human tumor cells. The present invention relates to methods of treating animals, specifically mammals, suffering from inflammatory, cardiovascular and/or neoplastic diseases by administering an amount of a balanoid or a pharmaceutically acceptable salt thereof to the animal. Human therapeutics are preferred.

The methods of the present invention comprise inhibiting protein kinase C activity by contacting protein kinase C with an inhibitory effective amount of a balanoid. Balanoids been discovered to inhibit the activity of protein kinase C. Exposure of cells *in vitro* to balanoids results in the inhibition of PKC activity. Inhibition of PKC activity in cells impedes cellular activities associated with several disease conditions. Of particular note is the selectivity exhibited by Balanoids which permits selective inhibition of one or more isoforms (isozymes) of PKC to a greater degree than other isoforms. Such selectivity has long been desired and is indicative of great therapeutic usefulness.

The methods of the present invention are useful in the treatment of diseases which involve cellular growth, regulation and differentiation such as inflammatory, cardiovascular and neoplastic diseases. PKC activity is associated with disease

conditions such as cancer, inflammation and reperfusion injury. Accordingly, the present invention relates to methods of treating a mammal suffering from cancer, inflammation such as the type associated with arthritis, reperfusion injury or other PKC-linked conditions. The methods comprise administering to the mammal an effective amount of a balanoid or a pharmaceutically acceptable salt thereof which inhibits PKC activity connected with disease.

PKC phosphorylates certain molecules, referred to herein as phosphorylation acceptor molecules. In order to identify compounds that inhibit PKC activity, an appropriate assay is performed. An exemplary and convenient assay is one in which radio labelled ATP is combined with a phosphorylation acceptor molecule in the presence of PKC and a balanoidal PKC inhibitor-candidate compound (hereinafter referred to as a "test compound"). Various amounts of test compound are used to determine the level of inhibitory activity that a particular test compound possesses. As a control, radio labelled ATP, phosphorylation acceptor molecule and PKC are combined without test compound. Assay conditions such as pH, salt and cofactor conditions are preferably maintained to be similar to physiological levels in order to duplicate *in vivo* conditions. In the assay, if PKC is active, the phosphorylation receptor molecule will be phosphorylated, gaining a radiolabelled phosphorus atom. Thus, the inhibitory activity of the test compound can be determined by incubating PKC, ^{32}P-ATP, phosphorylation receptor molecule and test compound and then measuring the level of phosphorylation activity by measuring the level of radioactive phosphorus present in the phosphorylation receptor molecule.

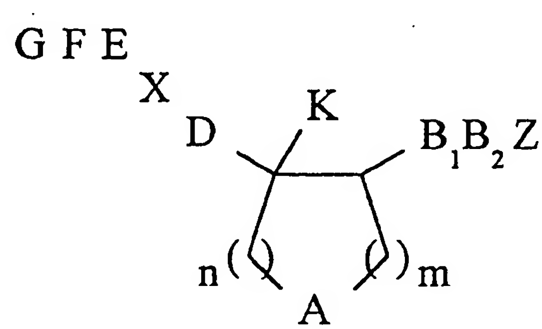
A convenient way to determine the selectivity of PKC inhibitory activity, test compounds are investigated for cAMP dependent protein kinase (PKA) inhibitory activity. As in the PKC assay, the level of inhibitory activity is determined by measuring the level of phosphorylation of a phosphorylation acceptor molecule incubated with radiolabelled ATP and PKA.

Preferred PKC inhibitors are selective inhibitors and do not effect the activity of PKA.

In order to investigate the effect that balanoid PKC inhibitors of the present invention have on cell growth and activity, assays are performed such as to determine human tumor cell growth inhibition, human keratinocyte inhibition and neutrophil superoxide anion release. Briefly, a human tumor cell growth inhibition assay measures the growth of tumor cells in the presence PKC inhibitors by measuring the incorporation of radiolabelled amino acid in cells. The human keratinocyte inhibition assay measures the proliferation of human epidermal keratinocytes in the same manner as tumor cell growth is measured. Hyperproliferation of keratinocytes is symptomatic of many disease conditions associated with inflammation. The neutrophil superoxide anion release assay measures a PKC inhibitors ability to block the PMA-induced effects on cells. The ability of the PKC inhibitors to affect superoxide release by PMA stimulated neutrophils is determined by measuring cytochrome c reduction. Cytochrome c is measured by measuring optical density.

In vivo studies to determine the anti-inflammatory activity of a test substance are conducted using the phorbol 12-myristate 13-acetate (PMA) induced mouse ear edema model which is a mouse model of acute inflammation. Using this model, the efficacy of various test compounds as anti-inflammatory agents are determined.

The compounds of the present invention are referred to herein as balanoids. Novel compounds according to the present invention can be expressed by the formula:



wherein:

A is: CH_2, NR^1, S, SO_2 or O;

B_1 is: NR^2, O or CH_2;

B_2 is: CO, CS, or SO_2;

Z is: R^4, aryl, heteroaryl, substituted aryl or substituted heteroaryl;

D is: NR^3, O or CH_2;

E is: R^5, aryl, heteroaryl, substituted aryl or substituted heteroaryl;

F is: CO, CS, $CH(OR^6)$, CH_2, O, S or NR^6;

G is: R^7, aryl, heteroaryl, substituted aryl, substituted heteroaryl or substituted cycloalkyl;

K is: hydrogen or lower alkyl;

X is: CO, CS, CH_2, CNR^8 or CCR^9R^{10};

R^1, R^2, R^3, R^4, R^6, R^7, R^8, R^9 and R^{10} are, independently, hydrogen, lower alkyl, aryl or JR^{11};

R^5 is: lower alkyl or aryl;

J is: CO, $C{=}NR^{12}$, SO_2 or P(O)O alkyl;

R^{11} is: hydrogen, lower alkyl, aryl, alkamino, arylamino, aryloxy or alkoxy;

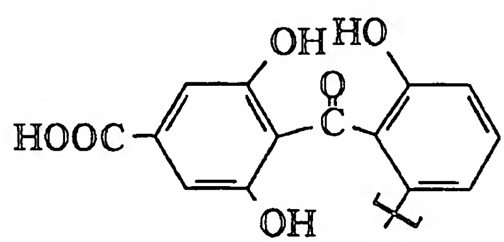
R^{12} is: straight or branched alkyl, aryl;

m is: 1-4;

n is: 1-4; and

m plus n is up to 5;

providing that if m is 3, A is NH, B_1 is O, B_2 is CO, Z is p-hydroxyphenyl, D is NH, X is CO, and E, F, and G, taken together, are



then n is not 1. Compounds according to the present invention include pharmaceutically acceptable salts of these compounds. Prodrugs, such as those having carbonates and esters of phenolic groups are also within the scope of the invention.

Lower alkyl means a straight chain, branched or cyclic moiety having from 1 to 6 carbon atoms.

Compounds according to the present invention can have at position A: CH_2, NR^1, S, SO_2 or O. It is preferred that A be NH, CH_2, or NR^1. When A is NR^1, it is preferred that R^1 be H or lower alkyl, aryl or JR^{1A} wherein J is CO, C=NH or SO_2 and R^{1A} is lower alkyl, aryl, alkylamino, arylamino, aryloxy or alkoxy. Thus, compounds of the present invention can have at position A: CH_2, NH, S, SO_2, O, NSO_2CH_3, NSO_2phenyl, NCONHphenyl, NCO phenyl, NCH_2phenyl, $NCH(CH_3)_2$, $NCOCH_3$, $NCOCF_3$, NSO_2-(5-dimethylamino-1-naphthalene, NSO_2-1-naphthalene, NSO_2-2-naphthalene, NSO_2-2-methyl-5-nitrophenyl, NSO_2-2-nitrophenyl, NSO_2-4-nitrophenyl, $NCH{=}NC(CH_3)_3$, $NCONHCH_3$, $NCO(CH_2)_{14}CH_3$, $NCOOCH_2$phenyl, $NCOOCH_2CH(CH_3)_2$, $NCOOC(CH_3)_3$, $NCOCH_2$phenyl, $NP{=}O(OCH_2CH_3)_2$, NCH_2CH_3, $NCOOCH_3$, NSO_2CH_2phenyl or $N(CH_2)_4OH$.

Compounds according to the present invention can have at position B_1: NR^2, O or CH_2. It is preferred that B_1 be NR^2 or O. B_1 is more preferably NH or NCH_3.

Compounds according to the present invention can have at position B_2: CO, CS, or SO_2. It is preferred that B_2 be CO or CS; B_2 is more preferably CO.

Compounds according to the present invention can have at position K: H, or lower alkyl, such as methyl, ethyl or propyl. It is preferred that K be H.

Compounds according to the present invention can have at position Z: R^4, aryl, heteroaryl, substituted aryl or substituted heteroaryl. In some embodiments, Z is preferably hydroxy substituted aryl, ether substituted aryl, hydroxy substituted heteroaryl or ether substituted aryl. In some embodiments, Z is pyridine, pyrrole, oxazole, indole, purine, furan, thiophene, pyridazine, pyrimidine, pyrazine, imidazole,

thiazole, isoxazole, pyrazole, isothiazole, benzene, methyl benzene, dimethyl benzene, trimethyl benzene, tetramethyl benzene, ethyl benzene, tetraethyl benzene, propyl benzene, tetrapropyl benzene, butyl benzene, tetrabutyl benzene, pentyl benzene, tetrapentyl benzene, methoxy benzene, dimethoxy benzene, trimethoxy benzene, tetramethoxy benzene, ethoxy benzene, diethoxy benzene, nitro benzene, dinitro benzene, halo benzene, dihalo benzene, trihalo benzene, tetrahalo benzene, benzene carboxylic acid, benzene dicarboxylic acid, benzamide, benzene diamide, 3,5-dihydroxy benzene, trihydroxy benzene, tetrahydroxy benzene, pentahydroxy benzene, triethoxy benzene, tetraethoxy benzene, propoxy benzene, dipropoxy benzene, tripropoxy benzene, tetra propoxy benzene, aniline, diamino benzene, methoxy pyridine, dimethoxy pyridine, hydroxy pyridine, dihydroxy pyridine, ethoxy pyrrole, dihydroxy pyrrole, dimethoxy indole, hydroxy purine, dimethoxy furan, hydroxy thiophene, methoxy pyridazine, dimethoxy pyridazine, hydroxy pyrimidine, diamido pyrimidine, amido pyrazine, cyanobenzene, butyloxybenzene, hydroxyindole, diethoxy pyrazine, phenyl, quinoline, methoxy quinoline, dimethoxy quinoline, trimethoxy quinoline, hydroxy quinoline, dihydroxy quinoline, ethoxy quinoline, amino quinoline, diamido quinoline, trihalo quinoline, quinoline carboxylic acid, quinazoline, methoxy quinazoline, dimethoxy quinazoline, trimethoxy quinazoline, hydroxy quinazoline, trihydroxy quinazoline, tetraethoxy quinazoline, diamino quinazoline, triamido quinazoline, tetrahalo quinazoline, quinazoline dicarboxylic acid. Z is more preferably p-hydroxy phenyl, p-benzyloxy phenyl, p-benzoate phenyl, p-carboxy phenyl, 4-(2-hydroxyphenylcarbonyl)-3,5-dihydroxy phenyl, p-amino phenyl, 4-fluoro phenyl, 4-benzyloxy phenyl, p-methyl phenyl, p-benzyloxycarbonyl phenyl, p-nitro phenyl, 5-benzyloxy-2-indole, 5-hydroxy-2-indole, 3,4-dihydroxy phenyl, 2-benzyloxy phenyl, 2-hydroxyphenyl, phenyl, p-$NHSO_2CH_3$phenyl, p-methoxymethyleneoxy phenyl, p-acetoxy phenyl. It is more preferred that Z be substituted phenyl. It is most preferred that Z be p-hydroxy phenyl, p-halophenyl or 5-hydroxy indole.

Compounds according to the present invention can have at position D: NR^3, O or CH_2. It is preferred that D be NR^3, or O. It is more preferred that D be O or NH.

Compounds according to the present invention can have at position E: R^4, aryl, heteroaryl, substituted aryl or substituted heteroaryl. In some embodiments, E is preferably hydroxy substituted aryl, ether substituted aryl, hydroxy substituted heteroaryl or ether substituted aryl. In other embodiments, E may be pyridine, pyrrole, oxazole, indole, purine, furan, thiophene, pyridazine, pyrimidine, pyrazine, imidazole, thiazole, isoxazole, pyrazole, isothiazole, benzene, methyl benzene, dimethyl benzene, trimethyl benzene, tetramethyl benzene, ethyl benzene, tetraethyl benzene, propyl benzene, tetrapropyl benzene, butyl benzene, tetrabutyl benzene, pentyl benzene, tetrapentyl benzene, methoxy benzene, dimethoxy benzene, trimethoxy benzene, tetramethoxy benzene, ethoxy benzene, diethoxy benzene, nitro benzene, dinitro benzene, halo benzene, dihalo benzene, trihalo benzene, tetrahalo benzene, benzene carboxylic acid, benzene dicarboxylic acid, benzamide, benzene diamide, 3,5-dihydroxy benzene, trihydroxy benzene, tetrahydroxy benzene, pentahydroxy benzene, triethoxy benzene, tetraethoxy benzene, propoxy benzene, dipropoxy benzene, tripropoxy benzene, tetra propoxy benzene, aniline, diamino benzene, methoxy pyridine, dimethoxy pyridine, hydroxy pyridine, dihydroxy pyridine, ethoxy pyrrole, dihydroxy pyrrole, dimethoxy indole, hydroxy purine, dimethoxy furan, hydroxy thiophene, methoxy pyridazine, dimethoxy pyridazine, hydroxy pyrimidine, diamido pyrimidine, amido pyrazine, diethoxy pyrazine, phenyl, quinoline, methoxy quinoline, dimethoxy quinoline, trimethoxy quinoline, hydroxy quinoline, dihydroxy quinoline, ethoxy quinoline, amino quinoline, diamido quinoline, trihalo quinoline, quinoline carboxylic acid, quinazoline, methoxy quinazoline, dimethoxy quinazoline, trimethoxy quinazoline, hydroxy quinazoline, trihydroxy quinazoline, tetraethoxy quinazoline, diamino quinazoline, triamido quinazoline, tetrahalo quinazoline, quinazoline dicarboxylic acid, 2-hydroxy benzene, 3-hydroxy

benzene, 3-butyloxy benzene, 3-butyloxy-5-hydroxy benzene, 3-hexanoyloxy-5-hydroxy benzene, 3,5-dioctyloxy benzene, 3-octyloxy-5-hydroxy benzene, 3-methoxy-5-hydroxy benzene, 3,5-bis(acetoxy)benzene, 3-(methoxycarbonyl)oxy-5-hydroxy benzene, 3,5-dihydroxy phenyl, 3-ethoxy-5-hydroxy phenyl, 3,5-dibenzyloxy phenyl, 3,5-dimethoxy phenyl, 3-hydroxy-5-benzoate phenyl, phenyl, 3,5-dimethoxymethyleneoxy phenyl, 3-methoxycarbonyloxy phenyl, 3-acetoxy-5-hydroxy phenyl. It is more preferred that E be 3,5-hydroxy benzene or 3-acyloxy-5-hydroxy benzene. It is most preferred that E be 3,5-hydroxy benzene.

Compounds according to the present invention can have at position F: CO, CS, $CH(OR^6)$, CH_2, O, S or NR^6. It is preferred that F be CO or CH_2. It is most preferred that F be CO.

Compounds according to the present invention can have at position G: R^4, aryl, heteroaryl, substituted aryl, substituted heteroaryl or substituted cycloalkyl. In some embodiments, G is preferably hydroxy substituted aryl, carboxy substituted aryl, hydroxy substituted heteroaryl or carboxy substituted heteroaryl. In other embodiments, G may be pyridine, pyrrole, oxazole, indole, purine, furan, thiophene, pyridazine, pyrimidine, pyrazine, imidazole, thiazole, isoxazole, pyrazole, isothiazole, benzene, methyl benzene, dimethyl benzene, trimethyl benzene, tetramethyl benzene, ethyl benzene, tetraethyl benzene, propyl benzene, tetrapropyl benzene, butyl benzene, tetrabutyl benzene, pentyl benzene, tetrapentyl benzene, methoxy benzene, dimethoxy benzene, trimethoxy benzene, tetramethoxy benzene, ethoxy benzene, diethoxy benzene, nitro benzene, dinitro benzene, halo benzene, dihalo benzene, trihalo benzene, tetrahalo benzene, benzene carboxylic acid, benzene dicarboxylic acid, benzamide, benzene diamide, 3,5-dihydroxy benzene, trihydroxy benzene, tetrahydroxy benzene, pentahydroxy benzene, triethoxy benzene, tetraethoxy benzene, propoxy benzene, dipropoxy benzene, tripropoxy benzene, tetra propoxy benzene, aniline, diamino benzene, methoxy pyridine, dimethoxy pyridine, hydroxy

pyridine, dihydroxy pyridine, ethoxy pyrrole, dihydroxy pyrrole, dimethoxy indole, hydroxy purine, dimethoxy furan, hydroxy thiophene, methoxy pyridazine, dimethoxy pyridazine, hydroxy pyrimidine, diamido pyrimidine, amido pyrazine, diethoxy pyrazine, phenyl, quinoline, methoxy quinoline, dimethoxy quinoline, trimethoxy quinoline, hydroxy quinoline, dihydroxy quinoline, ethoxy quinoline, amino quinoline, diamido quinoline, trihalo quinoline, quinoline carboxylic acid, quinazoline, methoxy quinazoline, dimethoxy quinazoline, trimethoxy quinazoline, hydroxy quinazoline, trihydroxy quinazoline, tetraethoxy quinazoline, diamino quinazoline, triamido quinazoline, tetrahalo quinazoline, quinazoline dicarboxylic acid, 2-cyano-6-hydroxy benzene, 2-hydroxy-5,6,7,8-tetrahydro-naphthalene, 2-acetoxy-6-carboxy benzene, 2-hydroxy-6-tetrazolyl benzene, 2-hydroxy-naphthalene, 2-hydroxy-6-(methoxycarbonyl) benzene, 2-carboxy-3-pyridinyl, 2-(ethoxycarbonyl)-6-hydroxy benzene, 2,3-dihydroxy benzene, 2-carboxy cyclohexane, 2,6-dihalo benzene, 2-acetoxy-6-(ethoxycarbonyl) benzene. In some embodiments, G is preferably 2-carboxy-6-hydroxy phenyl, 2-ethoxycarbonyl-6-hydroxy phenyl, 2-hydroxy phenyl, 2-benzyloxycarbonyl phenyl, 2-hydroxy naphthyl, 2,3,5,6,-tetramethyl phenyl, 2,6-dihydroxy phenyl, 2,6-dimethoxy phenyl, 2-carboxy cyclohexane, 2-hydroxy cyclohexane, 2-hydroxy-1-naphthyl, 2,6-dichloro phenyl, 2-methoxy-6-hydroxy phenyl, 2-carboxy-3-pyridine, 3-carboxy-2-pyridine, phenyl, 3,4-dihydroxy phenyl, 2-methoxycarbonyl-6-hydroxy phenyl, 2-butoxycarbonyl-6-hydroxy phenyl, 2-(2-methylpropyloxycarbonyl)-6-hydroxy phenyl, 2-nitrilo-6-hydroxy phenyl, 2-carboxy phenyl, 2-(4-acetoxybenzyloxycarbonyl)-6-hydroxy phenyl, 2-benzyloxycarbonyl-6-benzyloxy phenyl, 2,6-dibenzyloxy phenyl, 2-benzyloxycarbonyl cyclohexane, 1-benzyloxy-2-naphthyl, 2-methoxy-6-benzyloxy phenyl, 2-benzyloxycarbonyl-3-pyridinyl, 3-benzyloxycarbonyl-2-pyridinyl, 2-benzyloxyphenyl, 2-nitrilo-6-benzyloxy phenyl, 3,4-dibenzyloxyphenyl, 2-benzyloxy-1-naphthyl, 6-benzyloxy-2-tetrazolylphenyl, 6-hydroxy-2-tetrazolylphenyl, 2-methyltetrazolyl phenyl, 3-methylt trazolylphenyl, 2-hydroxy-1-

(5,6,7,8-tetrahydro) naphthyl, 3-benzyloxycarbonyl-4-benzyloxy phenyl, 3-carboxy-4-hydroxy phenyl, 2-methoxymethyleneoxy phenyl, 2-ethoxycarbonyl-6-benzyloxy phenyl, 2-benzyloxy carbonyl-1-naphthyl, 2-carboxy-1-naphthyl, 2-benzyloxy-6-methyl phenyl, 2-methyl-6-hydroxy phenyl, 2-acetoxy-6-ethoxycarbonyl phenyl, 2-cyclohexylmethoxycarbonyl-6-hydroxy phenyl, 2-carboxy-6-benzyloxy phenyl, 2-methoxycarbonyl-6-benzyloxy phenyl, 2-hexanoyloxy-6-carboxy phenyl. It is more preferred that G be 2-carboxy-6-hydroxyphenyl, 2-hydroxy-6-(tetrazol-2-y)phenyl, 2,6-dihydroxy phenyl, 2-hydroxy-1-naphthyl, 2-methoxycarbonyl-6hydroxyphenyl, 2-cyano-6-hydroxy phenyl, and 2-hydroxy-6-(trifluoromethylsulfonamino)phenyl. It is most preferred that G be 2-carboxy-6-hydroxy benzene and its ester or acyl derivatives as well as 2-R-6-hydroxyphenyl where R is carboxylic acid surrogate such as tetrazole or N-sulfonylcarboxamide.

Compounds according to the present invention can have at position X: CO, CS, CNR^8 or CCR^9R^{10}. It is preferred that X be CO or CH_2.

Compounds according to the present invention can have as R^1, R^2, R^3, R^4, R^6, R^7, R^8, R^9 and R^{10}, independently: hydrogen, lower alkyl, aryl or JR^{11} wherein J is CO, CN or SO_2 and R^{11} is lower alkyl, aryl, alkylamino, arylamino, aryloxy or alkoxy.

Compounds according to the present invention can have at position R^5 lower alkyl or aryl.

In compounds according to the present invention, m is 1-4. It is preferred that m be 1-2, preferably 1.

In compounds according to the present invention, n is 1-4. It is preferred that n be 1-3.

In compounds according to the present invention, n plus m is less than or equal to 5. It is preferred that n plus m is less than or equal to 4.

It will be appreciated that atoms within the moieties defined by n and m may have substituents. Such substituents may preferably include hydrocarbyl groups such as the lower alkyl groups, methyl, ethyl and propyl together with larger aliphatic and aromatic functions.

It will also be appreciated that m and n may contain other functional species such as carbonyl, thiocarbonyl, hydroxy, amino, halo and others. Preferred species are carbonyl and thiocarbonyl.

Preferred compounds contain aryl groups in positions Z, E and G. In preferred compounds, Z, E and G are hydroxy substituted aryl, ether substituted aryl, hydroxy substituted heteroaryl, or ether substituted aryl. E and G are preferably substituted aryls or substituted heteroaryls whereby the substitutions are located such that the two aryl rings are conformationally "crowded" out of plane with each other. Additionally, A is preferably NR^1 or CH_2.

Pharmaceutically acceptable salts of these compounds may be used in accordance with the present invention. One having ordinary skill in the art could readily appreciate what salts would be appropriate. Pharmaceutically acceptable salts include, but are not limited to sodium, trialkyl ammonium, potassium, calcium, zinc, lithium, magnesium, aluminum, diethanolamine, ethylenediamine, meglumine and acetate. Preferred salts are sodium and potassium.

In certain preferred compounds of the present invention A is CH_2, NR^1, S, or O; B1 is NR^2, O, or CH_2; B2 is CO or CS; Z is R^4, aryl, heteroaryl, substituted aryl or substituted heteroaryl or D is NR^3, O or CH_2; E is R^5, aryl, heteroaryl, substituted aryl or substituted heteroaryl; F is CO or CS; G is R^7, aryl, heteroaryl, substituted aryl or substituted heteroaryl; X is CO or CS; R^1, R^2, R^3, R^4, R^6, R^7, R^8, R^9 and R^{10} are, independently: hydrogen, lower alkyl or aryl; R^5 is lower alkyl or aryl; m is 1-4; and n is 1-4; where n plus m is less than or equal to 5.

In other preferred compounds of the present invention A is CH_2, NR^1, S, or O; B_1 is NR^2 or O; B_2 is CO or CS; Z is hydroxy substituted aryl, ether substituted aryl, hydroxy substituted heteroaryl, halo substituted aryl; D is NR^3 or O; E is hydroxy substituted aryl, ether substituted aryl, hydroxy substituted heteroaryl, acyloxy substituted aryl; F is CO or CS; G is hydroxy substituted aryl, ether substituted aryl,

hydroxy substituted heteroaryl, carboxy substituted aryl; X is CO or CS; R^1, R^2 and R^3 independently: hydrogen, lower alkyl or aryl; m is 1-2; and n is 1-3; where n plus m is less than or equal to 4.

In still other preferred compounds of the present invention A is NH, CH_2 or NR^1; B1 is NR^2 or O; B2 is CO or CS; Z is hydroxyphenyl or halophenyl; D is NR^3, O or CH_2; E is 3,5-hydroxy benzene or 3,5-alkoxy benzene; F is CO or CH_2; G is 2-carboxy-benzene, 2-hydroxy benzene, 2,6-dihydroxy benzene, 2-methoxy benzene, 2,6-dimethoxy benzene, or 6-hydroxy benzene-2-carboxylic acid; X is CO; R^1, R^2, or R^3 are, independently hydrogen, lower alkyl or aryl; m is 1; and n is 3.

In certain preferred compounds of the present invention A is NH or CH_2; B1 is NH; B2 is CO; Z is p-hydroxyphenyl; D is O; E is 3,5-hydroxy benzene; F is CO; G is 2-carboxy-6-hydroxyphenyl, 2-hydroxy-6-(tetrazol-2-y)phenyl, 2,6-dihydroxy phenyl, 2-hydroxy-1-naphthyl, 2-methoxycarbonyl-6hydroxyphenyl, 2-cyano-6-hydroxy phenyl, and 2-hydroxy-6-(trifluoromethylsulfonamino)phenyl; X is CO; m is 1; and n is 3.

As will be appreciated, it is generally the case that one stereoisomer is more biologically active than its enantiomer. It is envisioned that preferred stereoisomerism will be determined for active species and that such preferred compounds will be selected for therapeutic and other uses.

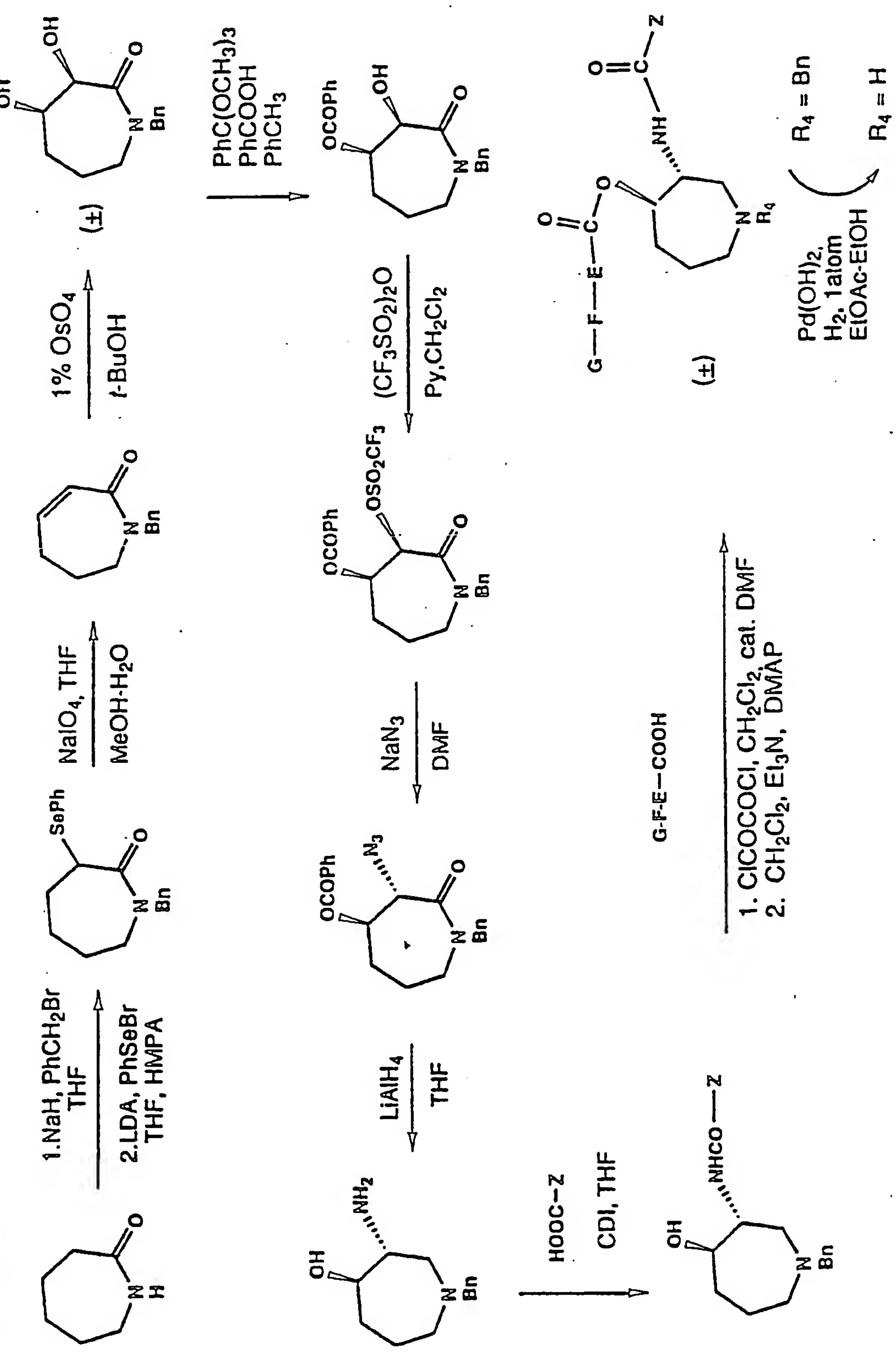
Compounds of the present invention may be synthesized from readily available starting materials by standard techniques such as by following the basic synthesis set out below. One having ordinary skill in the art may employ other well known synthetic schemes to produce compounds according to the present invention.

Prodrugs such as carbonates and carboxy esters of phenolic OH and NH groups can be prepared by the derivatization of OH and NH groups with acylating agents, such as methyl chloroformate, ethyl chloroformate, isobutyryl chloride, methoxypropionyl chloride, methyl chlorosuccinate, ethyl chlorosuccinate and benzoyl chloride, for example.

Additionally, prodrugs of compounds which contain a carboxylic acid can be prepared by derivitazation with alkylating agents, such as methyl iodide or acetoxymethyl chloride.

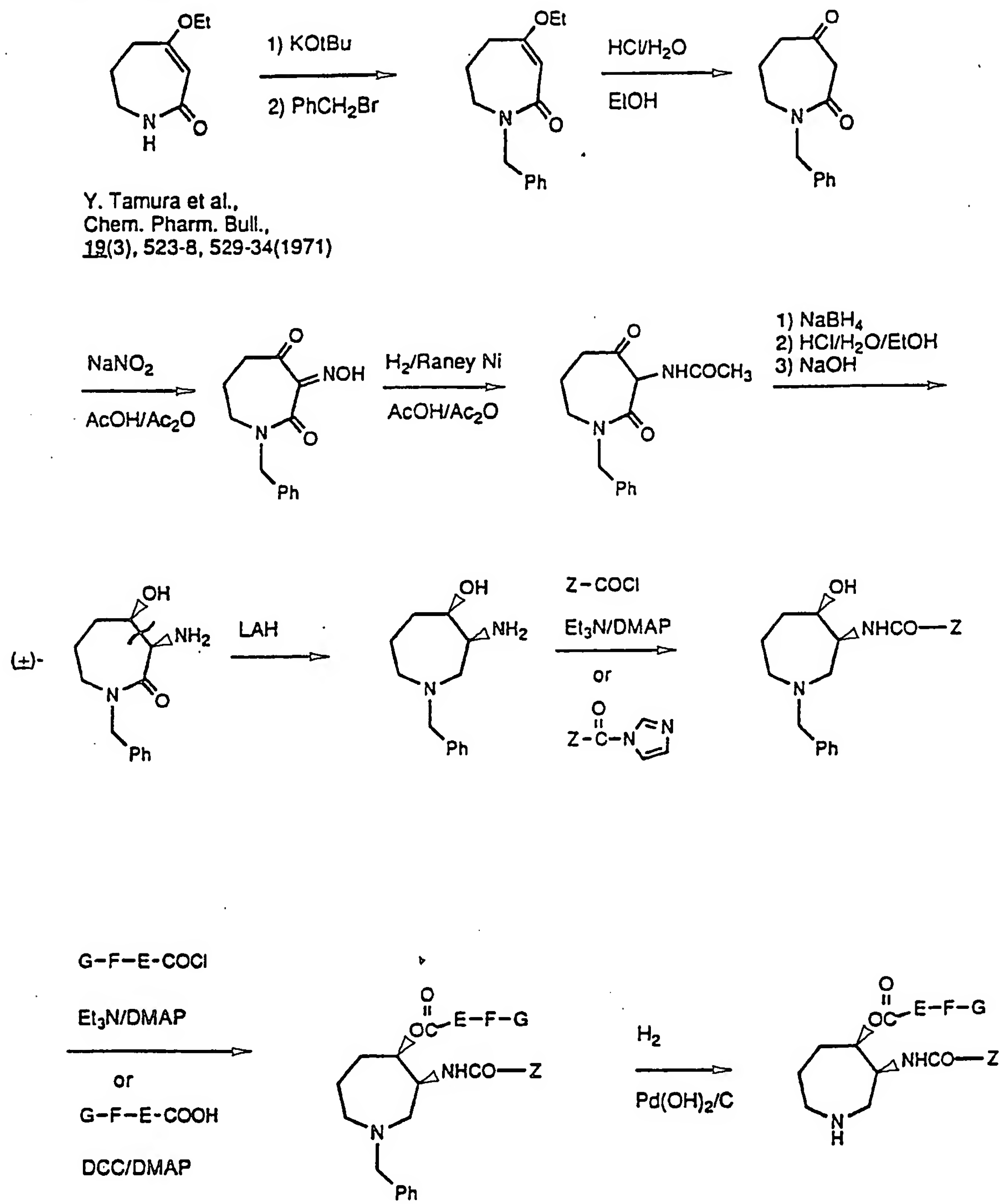
Reaction Scheme I provides syntheses for producing compounds according to the present invention including the use of a cyclic carbonyl or a heterocyclic carbonyl such as the seven membered lactam shown as a starting material. For example, a lactam can be benzylated with base in tetrahydrofuran to protect the nitrogen functionality. It is then reacted with base and phenylselenyl chloride followed by sodium periodate to yield the unsaturated lactam. Oxidation with osmium tetroxide followed by benzoylation yields the hydroxy benzoate shown. Further reaction with trifluoromethanesulfonic anhydride and sodium azide provides the anti azido ester which can be reduced with, for example, lithium aluminum hydride. Reaction with a carboxylic acid substituted with a Z functionality yields the amide. Further reaction with a GFE carboxylic function followed by deprotection provides the family of ester/amides.

Scheme I



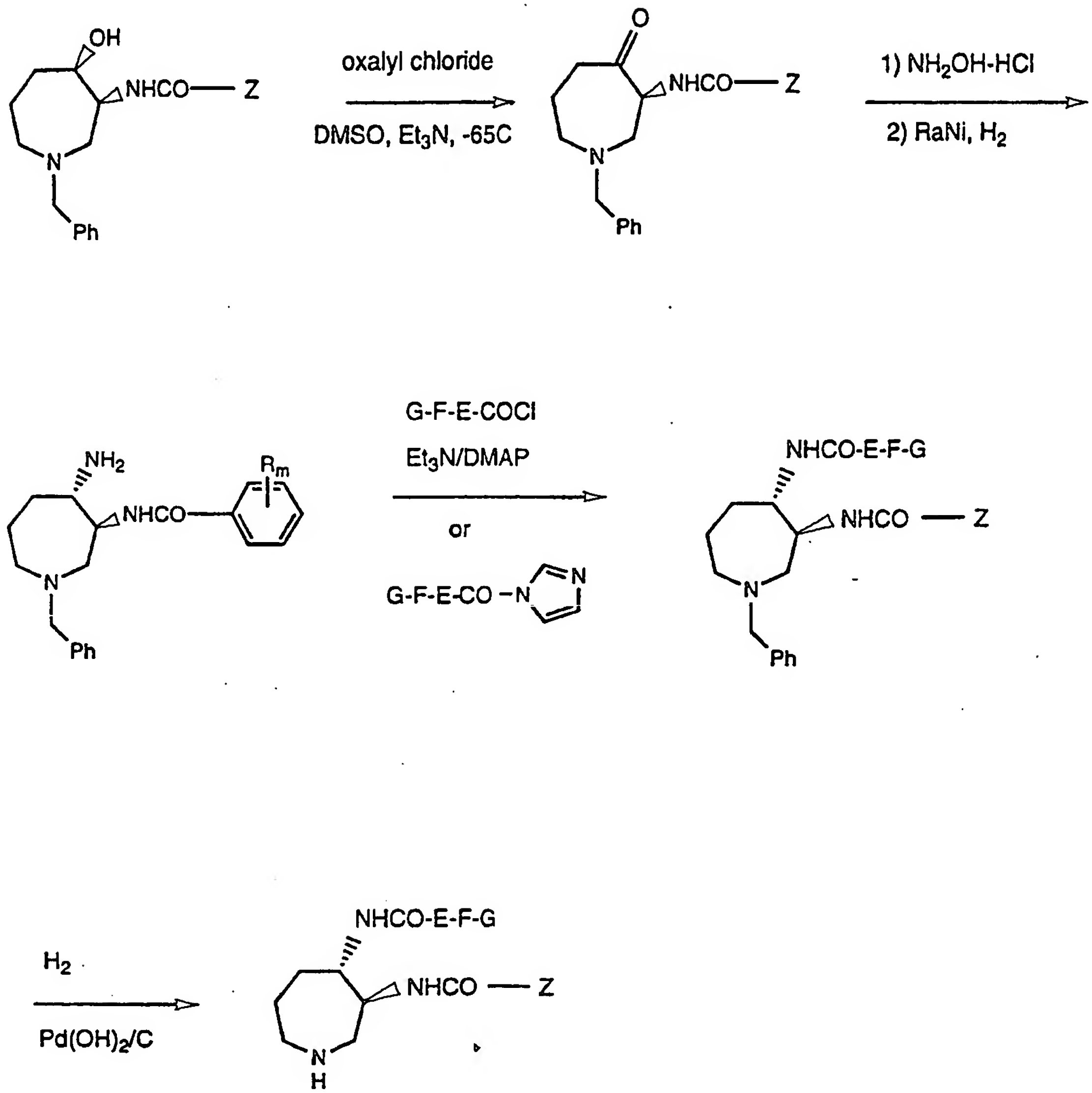
Scheme II provides a synthesis scheme for producing compounds according to the present invention including the use of an enol ether lactam such as the azepinone shown as a starting material. For example, an enolether lactam can be benzylated with base in tetrahydrofuran to protect the nitrogen function. It is then hydrolyzed with acid and reacted with sodium nitrite in acetic acid to form the oxime. Catalytic hydrogenation in the presence of acetic anhydride gives the acetamide, which can be reduced with, for example, sodium borohydride and hydrolyzed to the syn (or anti) aminohydroxy lactam. Reduction with, for example, lithium aluminum hydride and reaction with a carboxylic acid substituted with a Z functionality yields the amide, which can be further reacted with GFE carboxylic function and deprotected to provide the family of ester/amides.

Scheme II


OEt
1) KOtBu
2) PhCH2Br
HCl/H2O
EtOH
Y. Tamura et al.,
Chem. Pharm. Bull.,
19(3), 523-8, 529-34(1971)
NaNO2
AcOH/Ac2O
NOH
H2/Raney Ni
AcOH/Ac2O
NHCOCH3
1) NaBH4
2) HCl/H2O/EtOH
3) NaOH
(±)-
OH
NH2
LAH
Z-COCl
Et3N/DMAP
or
NHCO—Z
G-F-E-COCl
Et3N/DMAP
or
G-F-E-COOH
DCC/DMAP
E-F-G
H2
Pd(OH)2/C
Ph

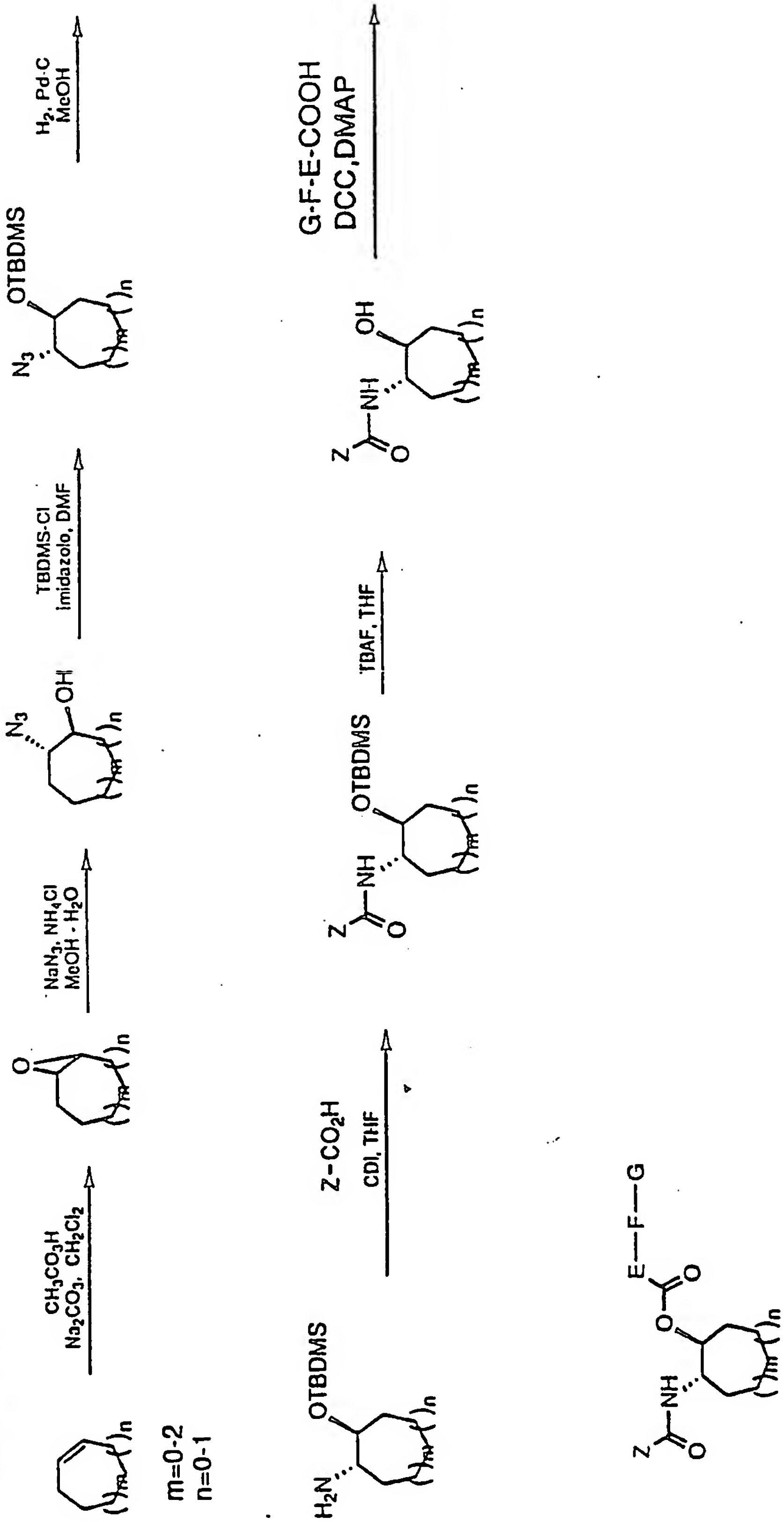
Reaction Scheme III provides methods for producing compounds according to the present invention including the use as a starting material of the previously mentioned syn aminohydroxy lactam. Oxidation of the alcohol using, for example, oxalyl chloride, dimethylsulfoxide, and triethylamine (Swen oxidation) provides the Keto intermediate which is treated with $HONH_2$-HCl followed by reduction using, for example, RaNi (Raney nickel) catalyst and hydrogen affords the amino-amide. Reaction with a GFE carboxylic acid function followed by deprotection provides the family of diamides.

Scheme III


OH
NHCO — Z
N
Ph
oxalyl chloride
DMSO, Et3N, -65C
O
NHCO — Z
N
Ph
1) NH2OH-HCl
2) RaNi, H2
NH2
Rm
NHCO
N
Ph
G-F-E-COCl
Et3N/DMAP
or
G-F-E-CO – N
N
NHCO-E-F-G
NHCO — Z
N
Ph
H2
Pd(OH)2/C
NHCO-E-F-G
NHCO — Z
N
H

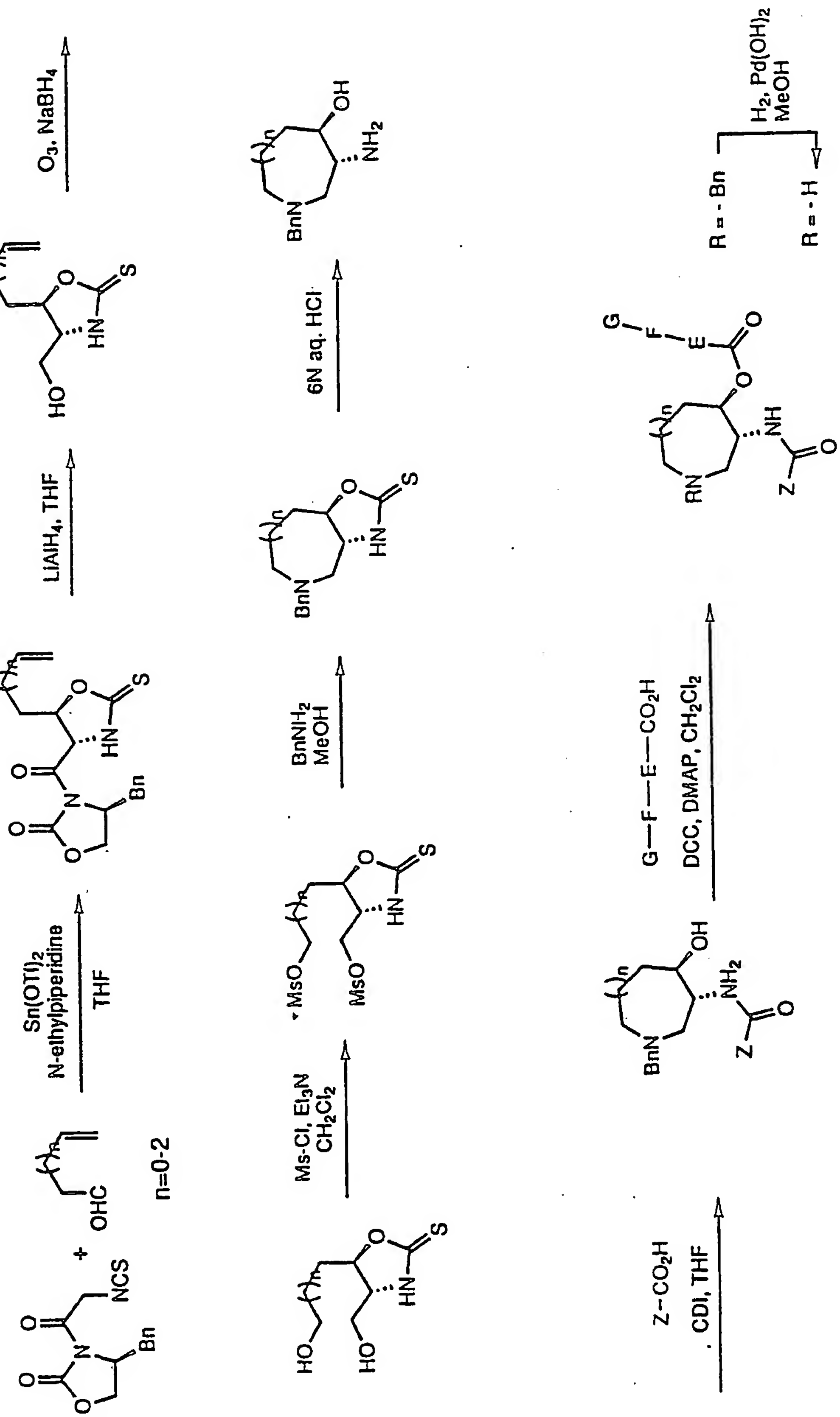
Scheme IV provides a synthesis scheme for producing compounds according to the present invention including the use as a starting material of a cyclic olefin as shown. Epoxidation with peracetic acid followed by reaction with sodium azide affords the anti azido alcohol, which is O-protected and reduced to the aminoalcohol ether. Reaction with a carboxylic acid substituted with a Z functionality yields the amide, which is O-deprotected and reacted with a GFE carboxylic function to provide the family of ester/amides.

Scheme IV


m=0-2
n=0-1
CH_3CO_3H
Na_2CO_3, CH_2Cl_2
NaN_3, NH_4Cl
MeOH - H_2O
TBDMS-Cl
Imidazole, DMF
H_2, Pd-C
MeOH
OTBDMS
N_3
OH
H_2N
Z-CO_2H
CDI, THF
TBAF, THF
G-F-E-COOH
DCC,DMAP
Z
NH
O
E
F
G

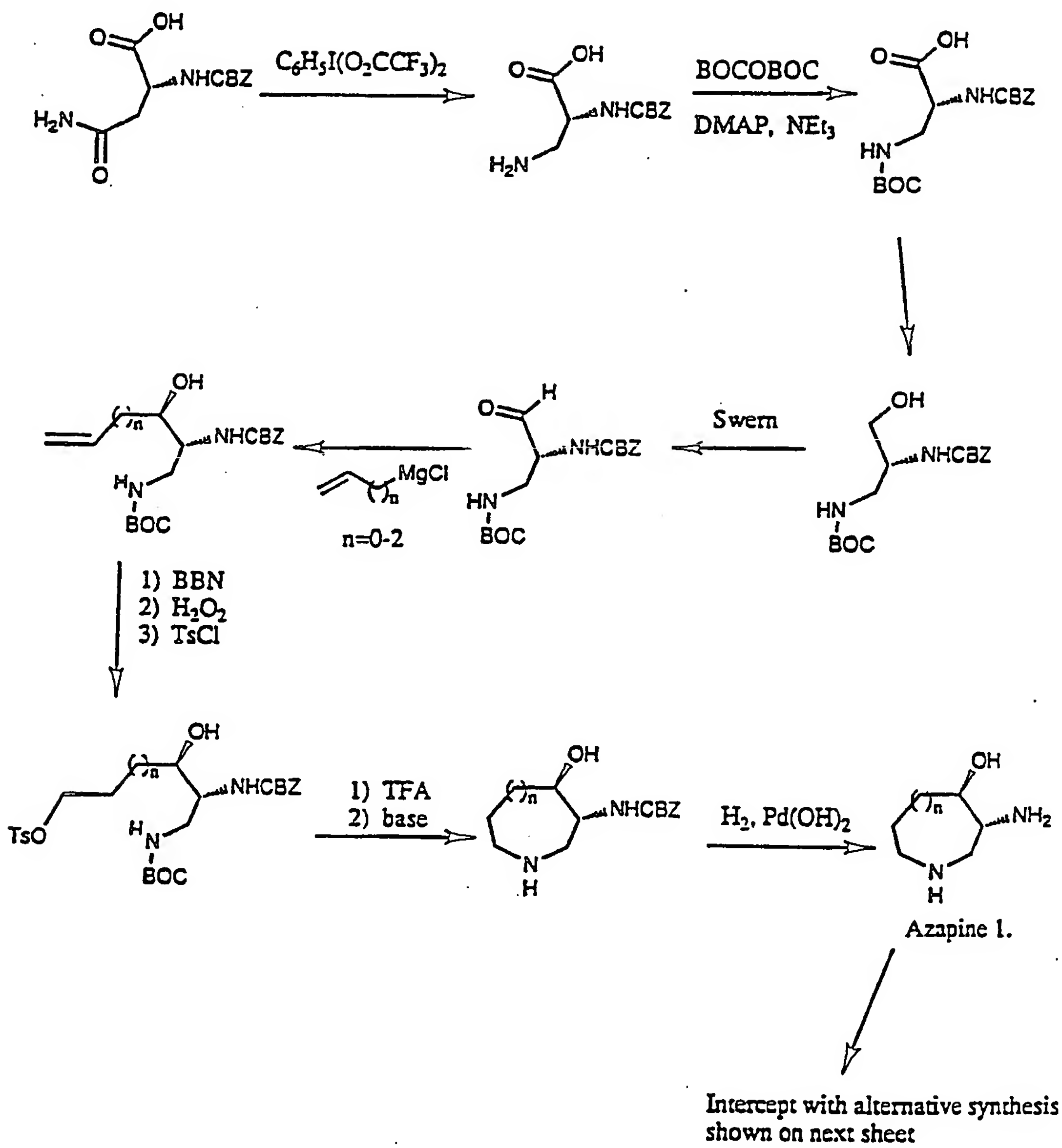
Scheme V provides a syntheses for preparing compounds according to the present invention including a synthesis scheme for producing 6, 7 and 8 member cyclic and heterocyclic groups including B_1 and D with stereo specific attachment, including the use as a starting material of the unsaturated aldehyde. For example, tin-mediated condensation and subsequent cyclization of the aldehyde with an isothiocyanate affords the oxazolidine thione, which can be reduced with lithium aluminum hydride, ozonolyzed, and further reduced with, for example, sodium borohydride to the diol. Mesylation with methanesulfonyl chloride and base followed by ring closure with benzylamine affords the azepine, which is hydrolyzed with an acid, for example, hydrochloric acid. The resultant anti aminoalcohol is reacted with a carboxylic acid substituted with a Z functionality to give the amide, which is further reacted with a GFE carboxylic function and deprotected to provide the family of ester/amides with predictable stereochemistry at the positions of attachment of B_1 and D to the ring system.

Scheme V


n=0-2
Sn(OTf)2
N-ethylpiperidine
THF
LiAlH4, THF
O3, NaBH4
Ms-Cl, Et3N
CH2Cl2
BnNH2
MeOH
6N aq. HCl
Z-CO2H
CDI, THF
G—F—E—CO2H
DCC, DMAP, CH2Cl2
R = - Bn
H2, Pd(OH)2
MeOH
R = - H

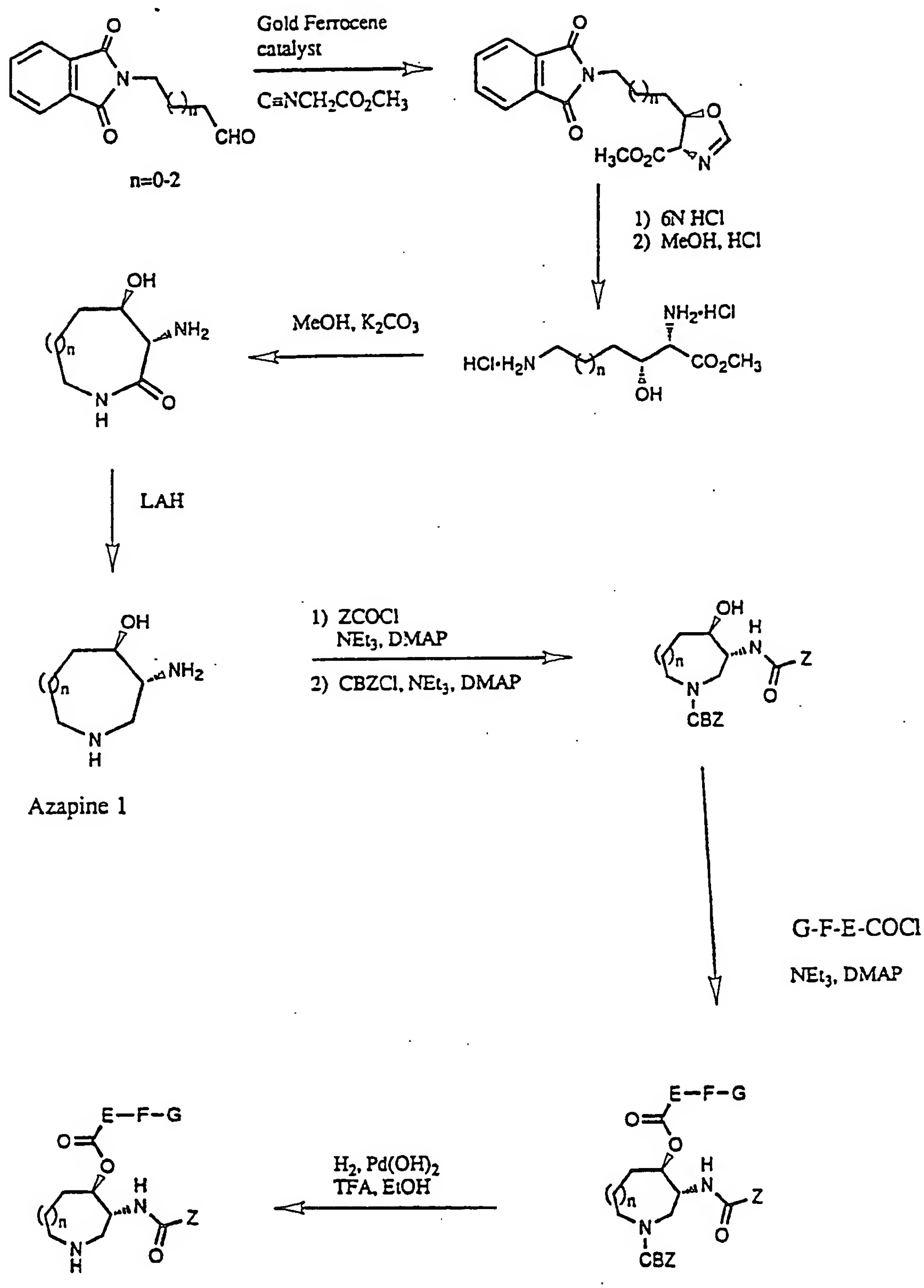
The reactions of Scheme VI provide a synthesis scheme for producing 6, 7, and 8 membered cyclic and heterocyclic groups including B_1 and D with stereo specific attachment including the use as a starting material of N-carbobenzyloxy asparagine. For example, CBZ-asparagine is reacted with bis(trifluoroacetoxy) iodobenzene to give the mono-protected diaminoacid, which is differentially protected with di-t-butyl dicarbonate and reduced with, for example, borane/tetrahydrofuran. Oxidation to the aldehyde and condensation with an unsaturated organometallic affords the diprotected diamino alcohol, which gives the terminal tosyloxy compound after hydroboration/oxidation and treatment with toluene sulfonyl chloride. Removal of the butoxycarbonyl is accomplished by acid treatment, for example, formic acid or trifluoroacetic acid, followed by removal of the amine-protecting group, which can be removed with hydrogen. Selective reaction with a carboxylic acid substituted with a Z functionality followed by treatment with benzyl chloroformate and base gives the protected amide, which is further reacted with a GFE carboxylic function and deprotected to provide the family of ester/amides with predictable stereochemistry at the positions of attachment of B_1 and D to the ring system.

Scheme VI


OH
O
NHCBZ
H_2N
O
$C_6H_5I(O_2CCF_3)_2$
OH
O
NHCBZ
H_2N
BOCOBOC
DMAP, NEt_3
O
OH
NHCBZ
HN
BOC
OH
NHCBZ
HN
BOC
Swern
O
H
NHCBZ
HN
BOC
MgCl
n
n=0-2
OH
n
NHCBZ
HN
BOC
1) BBN
2) H_2O_2
3) TsCl
OH
n
NHCBZ
TsO
HN
BOC
1) TFA
2) base
OH
n
NHCBZ
N
H
H_2, $Pd(OH)_2$
OH
n
NH_2
N
H
Azapine 1.
Intercept with alternative synthesis
shown on next sheet

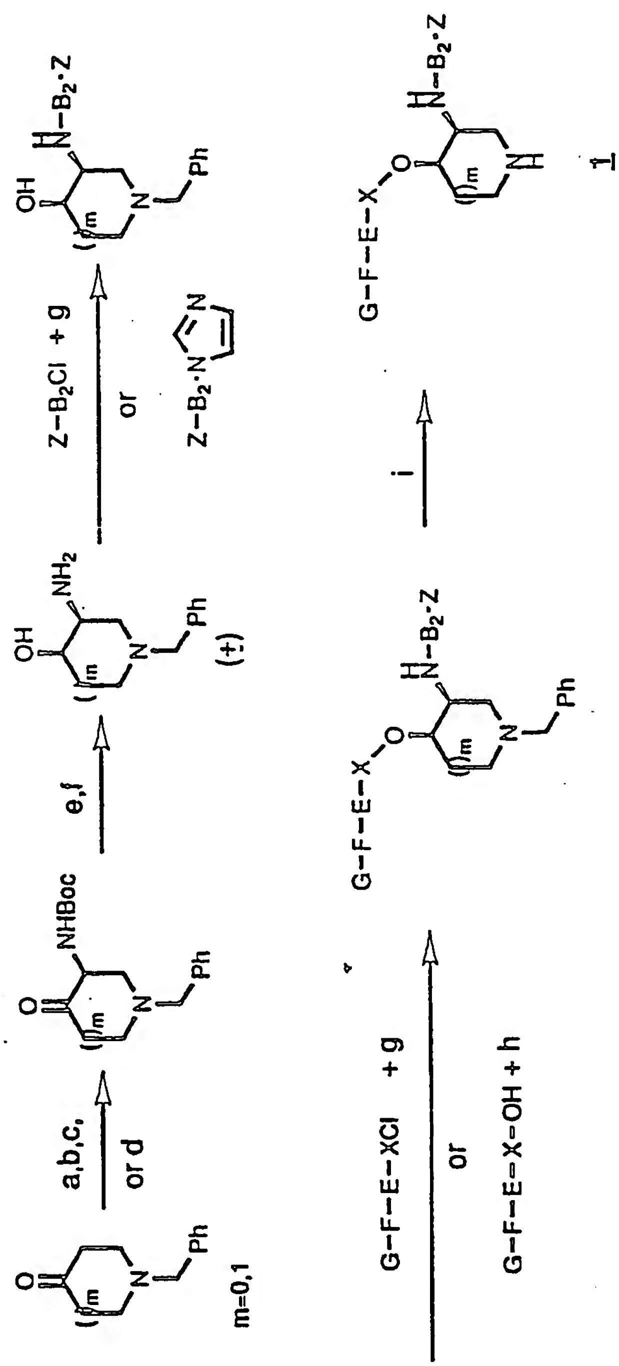
Scheme VII provides a syntheses for producing compounds according to the present invention including a synthesis scheme for producing 6, 7, and 8 member cyclic and heterocyclic groups including B_1 and D with stereo specific attachment including the use as a starting material of phthalimide alkyl aldehyde. for example, the aldehyde can be reacted with methyl isocyanoacetate in the present of gold ferrocene catalyst to give the oxazolidine, which is hydrolyzed to the diaminohydroxy ester salt with for example, hydrochloric acid. Base mediated cyclization affords the lactam, which can be reduced to an aminohydroxy compound. Reaction with a carboxylic acid substituted with a Z functionality followed by treatment with benzyl chloroformate and base gives the protected amide, with is further reacted with a GFE carboxylic function and deprotected to provide the family of ester/amides with predictable stereo chemistry at the positions of attachment of B_1 and D to the ring system.

Scheme VII


Gold Ferrocene catalyst
CNCH2CO2CH3
CHO
n=0-2
H3CO2C
1) 6N HCl
2) MeOH, HCl
MeOH, K2CO3
NH2•HCl
HCl•H2N
CO2CH3
OH
NH2
LAH
1) ZCOCl
NEt3, DMAP
2) CBZCl, NEt3, DMAP
CBZ
Azapine 1
G-F-E-COCl
NEt3, DMAP
E—F—G
H2, Pd(OH)2
TFA, EtOH

Scheme VIII A provides a synthesis scheme for producing compounds according to the present invention including a synthesis scheme for producing 5 and 6 member cyclic and heterocyclic groups including B_1 and D with syn attachment including the se of the protected cyclic ketone as starting material. For example, the ketone is deprotonated and the enolate aminated to afford the butoxycarbonylamino ketone which can be stereo specifically reduced with, for example, sodium borohydride to the syn aminoalcohol. Reactions with a carboxylic acid substituted with a Z functionality yields the amide. Further reaction with a GFE carboxylic function followed by deprotection provides the family of syn ester/amides.

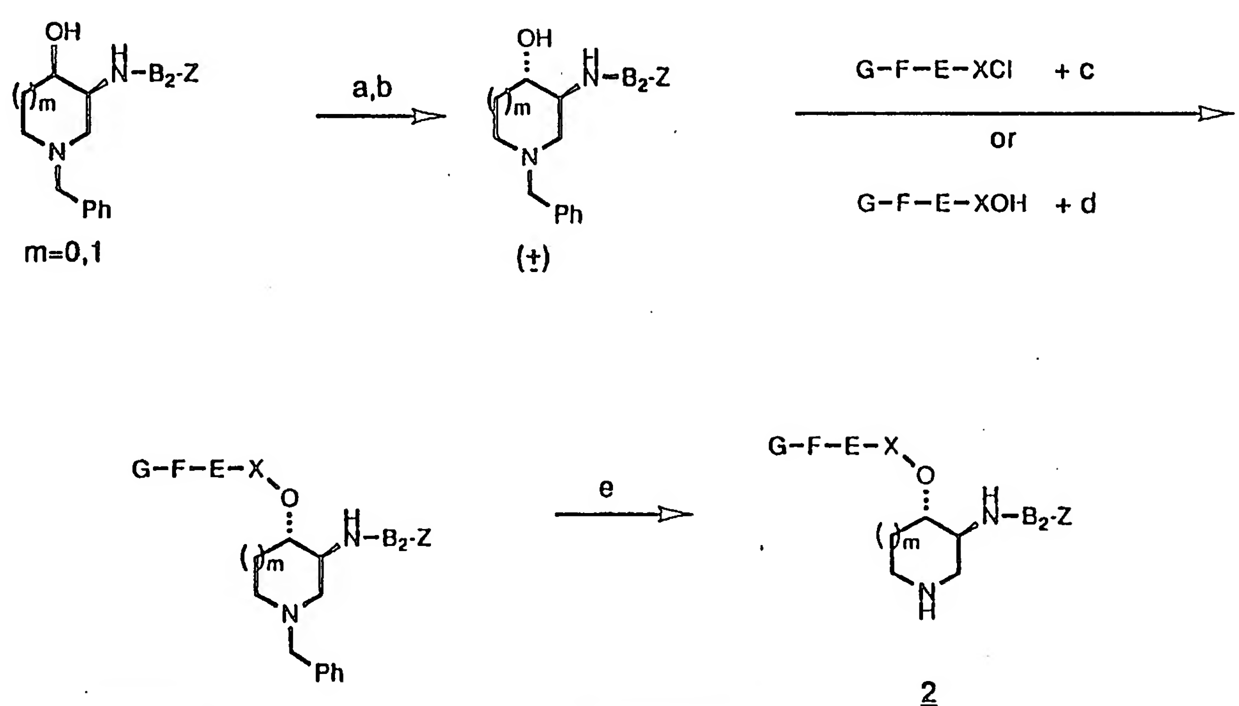
Scheme VIII A



a) Li(NSi$_3$)$_2$ or LDA, b) di-*tert*-butyl azodicarboxylate, c) Zn / H$^+$, d) Li-N(Boc)OTs, e) NaBH$_4$, f) H$^+$, g) Et$_3$N / DMAP, h) DCC / DMAP, i) H$_2$ / Pd(OH)$_2$ / C

Scheme VIII B provides a synthesis scheme for producing compounds according to the present invention including a synthesis scheme for producing 5 and 6 member cyclic and heterocyclic groups including B_1 and D with anti attachment including the use as starting material of the syn hydroxyamide from Scheme VIII A. For example, the syn hydroxyamide can be inverted to anti hydroxyamide by treatment with carboxylic acid, such as acetic acid, in the present of triphenylphosphine and diethylazodicarboxylate followed by treatment with sodium methoxide. Reaction with a GFE carboxylic function followed by deprotection provides the family of anti ester/amides.

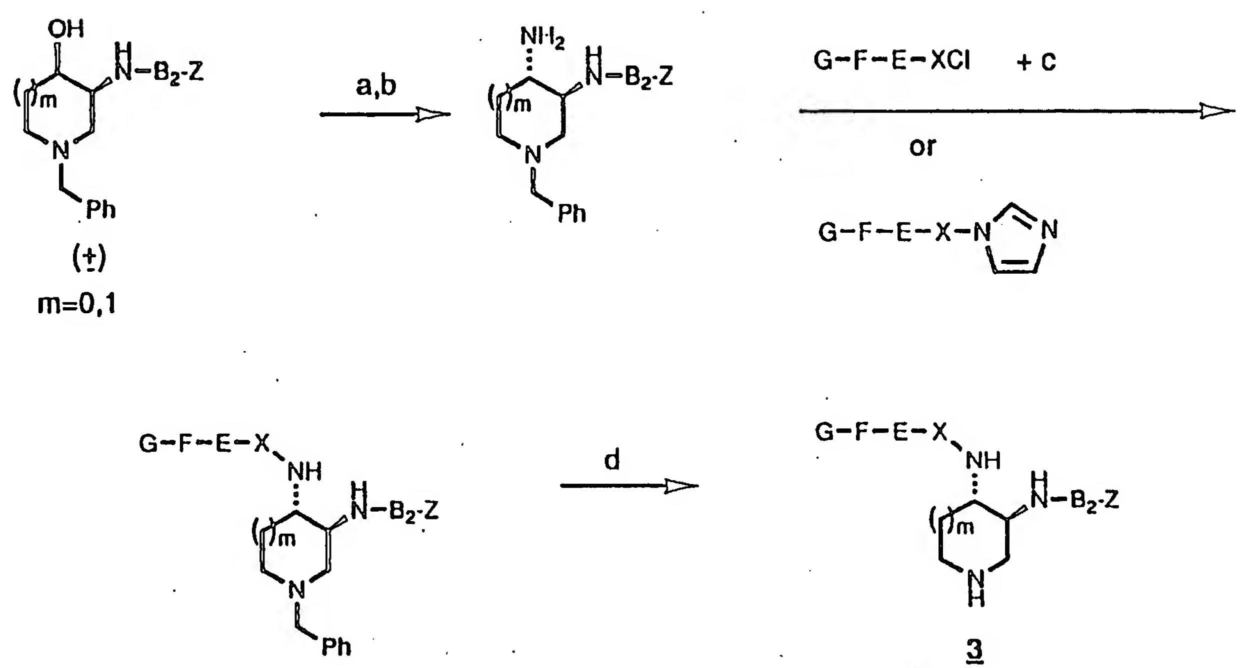
Scheme VIII B



a) CH_3CO_2H / Ph_3P / DEAD, b) $NaOCH_3$, c) Et_3N / DMAP, d) DCC / DMAP, e) H_2 / $Pd(OH)_2$ / C

Scheme VIII C provides methods for producing compounds according to the present invention including a synthesis scheme for producing 5 and 6 member cyclic and heterocyclic groups including B_1 and D with anti attachment including the use as starting material of the syn hydroxyamide from Scheme VIII A. For example, the syn hydroxyamide can be inverted to anti amino amide by treatment with trifluoromethane sulfonic anhydride and sodium azide followed by reduction with, for example, tin (II) chloride. Reaction with a GFE carboxylic function followed by deprotection provides the family of anti diamides.

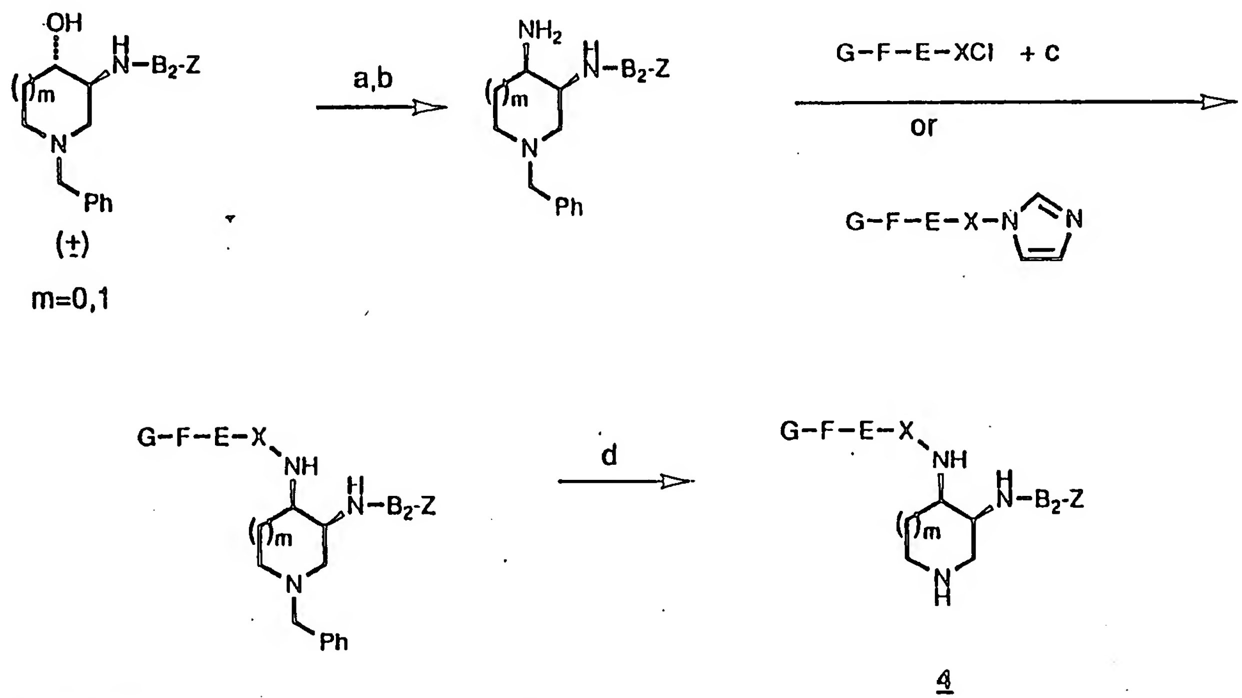
Scheme VIII C



a) $PO(OPh)_2N_3$ / DEAD / PPh_3 or Tl_2O / NaN_3, b) PPh_3 / H_2O or $SnCl_2$, c) Et_3N / DMAP, d) H_2 / $Pd(OH)_2$ / C

Scheme VIII D provides a synthesis scheme for producing compounds according to the present invention including a synthesis scheme for producing 5 and 6 member cyclic and heterocyclic groups including B_1 and D with syn attachment including the use as starting material of the anti hydroxyamide from Scheme VIII B. For example, the anti hydroxyamide can be inverted to syn amino amide by treatment with trifluoromethanesulfonic anhydride and sodium azide followed by reduction with, for example, tin (II) chloride. Reaction with a GFE carboxylic function followed by deprotection provides the family of syn diamides.

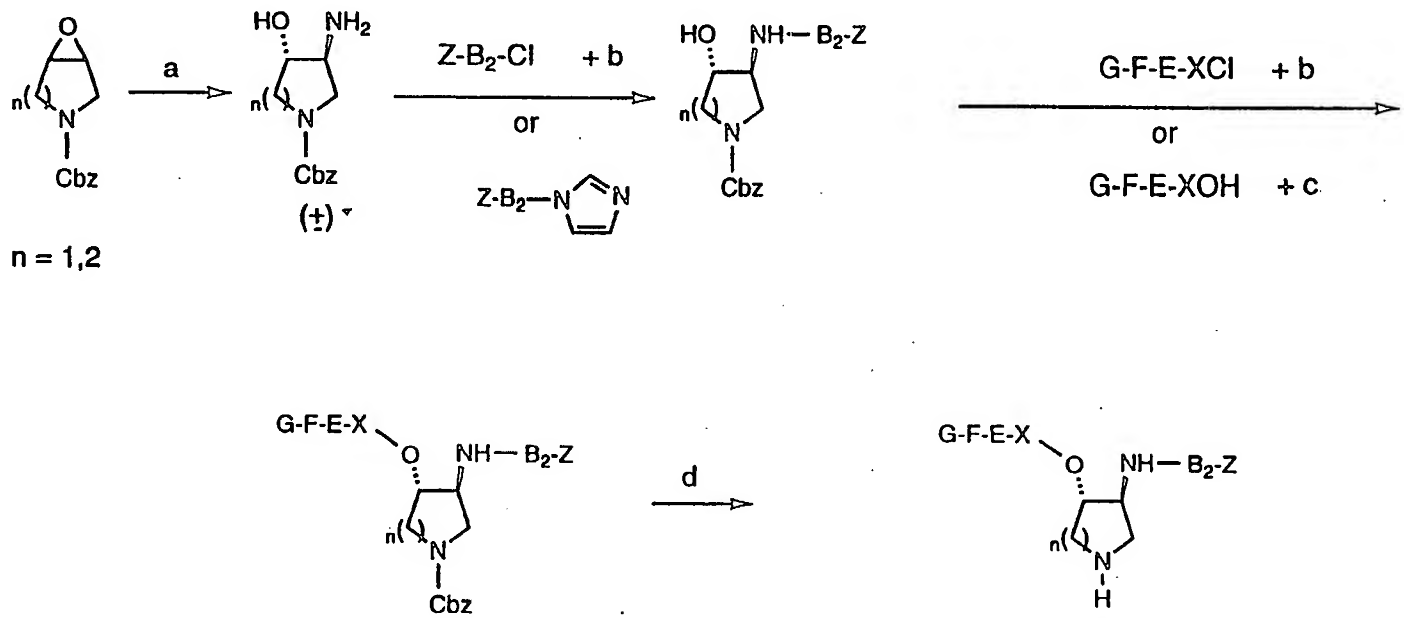
Scheme VIII D



a) $PO(OPh)_2N_3$ / DEAD / PPh_3 or Tl_2O / NaN_3, b) PPh_3 / H_2O or $SnCl_2$, c) Et_3N / DMAP, d) H_2 / $Pd(OH)_2$ / C

Scheme VIII E provides a synthesis scheme for producing compounds according to the present invention including producing 5 and 6 member cyclic and heterocyclic groups including B_1 and D with anti attachment including the use of the protected cyclic epoxide as starting material. For example, the epoxide is opened with ammonia to provide the anti aminoalcohol or with azide to provide the azido-alcohol. Reduction of the latter with, for example, triphenylphosphine provides the amino alcohol. Reaction with a carboxylic acid substituted with a Z functionality yields the anti hydroxyamide. Further reaction with a GFE carboxylic function followed by deprotection provides the family of anti ester/amides.

Scheme VIII E

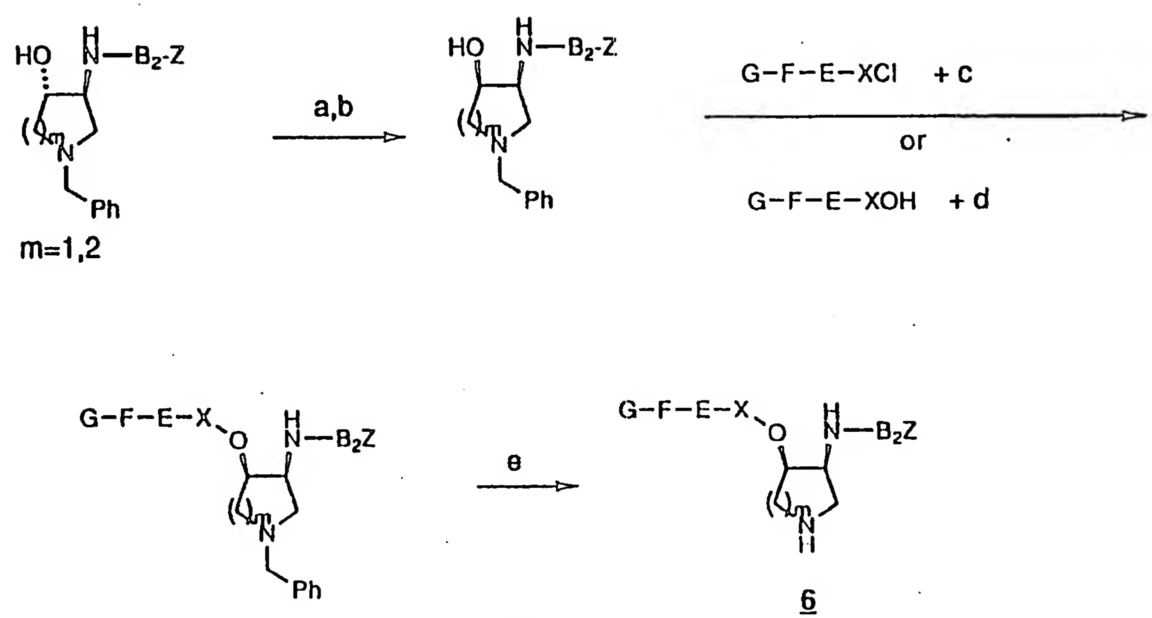


5

a) NH_3, or i) NaN_3, ii) Ph_3P, iii) 0.5 N NaOH,
b) Et_3N / DMAP, c) DCC / DMAP, d) H_2 /$Pd(OH)_2$ / C

Scheme VIII F provides a synthesis scheme for producing compounds according to the present invention including a synthesis scheme for producing 5 and 6 member cyclic and heterocyclic groups including B_1 and D with syn attachment including the use of the anti hydroxyamide from Scheme VIII E as starting material. For example, the anti hydroxyamide can be inverted to syn hydroxyamide by treatment with carboxylic acid, such as acetic acid in the presence of triphenylphosphine and diethyl azodicarboxylate followed by deprotection provides the family of syn ester/amides.

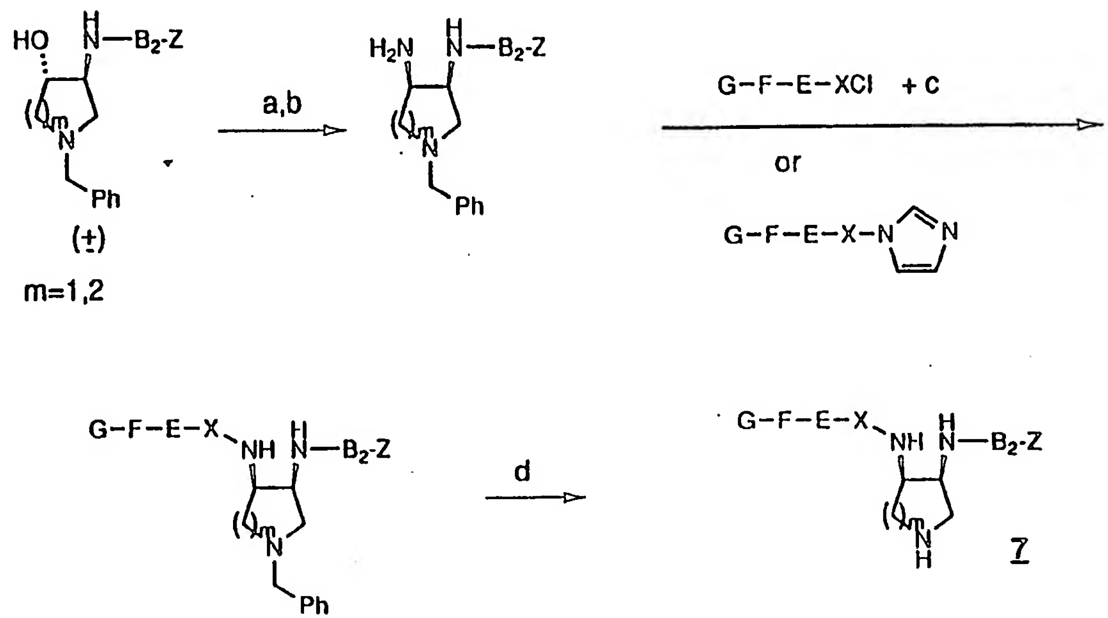
Scheme VIII F



a) CH_3CO_2H / Ph_3P / DEAD, b) $NaOCH_3$, c) Et_3N / DMAP, d) DCC / DM AP, e) H_2 / $Pd(OH)_2$ / C

Scheme VIII G provides a synthesis scheme for producing compounds according to the present invention including a synthesis scheme for producing 5 and 6 member cyclic and heterocyclic groups including B_1 and D with syn attachment including the use of the anti hydroxyamide from Scheme VIII E as starting material. For example, the anti hydroxyamide can be inverted to syn amino amide by treatment with trifluoromethanesulfonic anhydride and sodium azide followed by reduction with, for example, tin (II) chloride. Reaction with a GFE carboxylic function followed by deprotection provides the family of syn diamides.

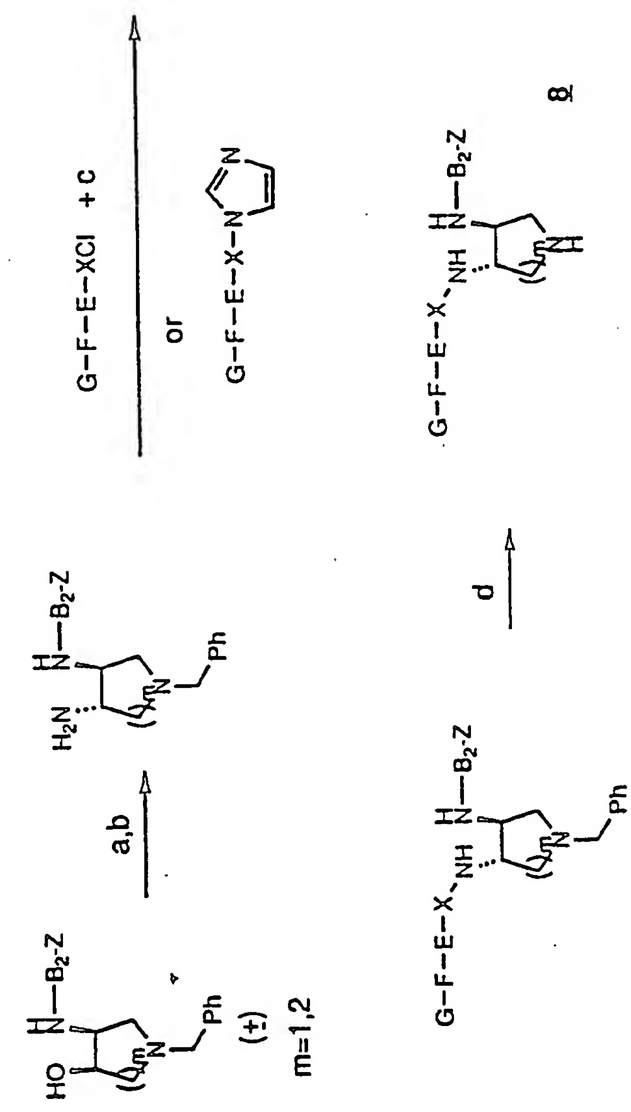
Scheme VIII G



a) $PO(OPh)_2N_3$ / DEAD / PPh_3 or Tl_2O / NaN_3, b) PPh_3 / H_2O or $SnCl_2$, c) Et_3N / DMAP, d) H_2 / $Pd(OH)_2$ / C

Scheme VIII H provides a synthesis scheme for producing compounds according to the present invention including a synthesis scheme for producing 5 and 6 member cyclic and heterocyclic groups including the use of the syn hydroxyamide from Scheme VIII F as starting material. For example, the syn hydroxyamide can be inverted to anti amino amide by treatment with trifluoromethanesulfonic anhydride and sodium azide followed by reduction with, for example, tin (II) chloride. Reaction with a GFE carboxylic function followed by deprotection provides the family of anti diamides.

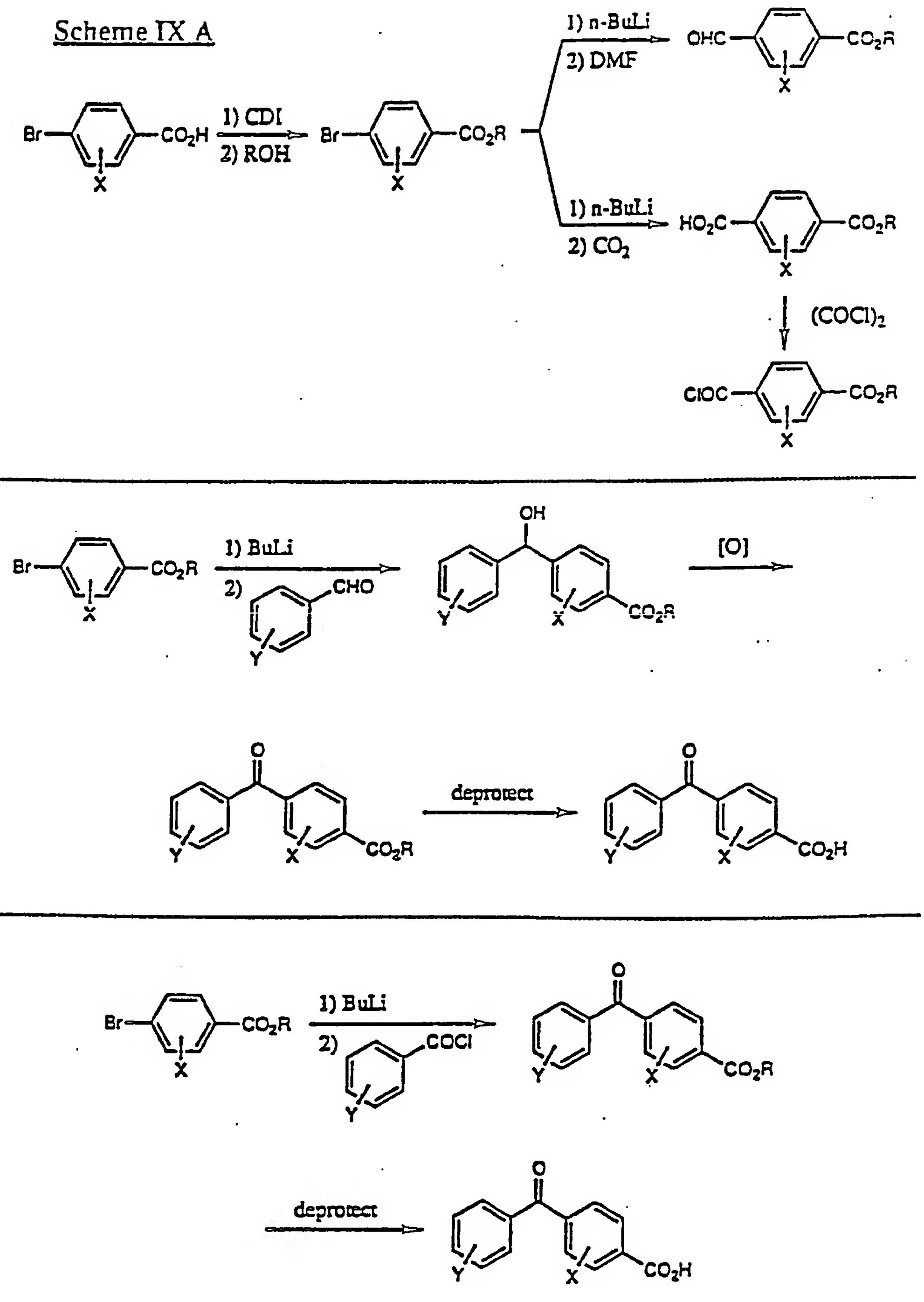
Scheme VIII H



a) PO(OPh)$_2$N$_3$ / DEAD / PPh$_3$ or Tf$_2$O / NaN$_3$, b) PPh$_3$ / H$_2$O or SnCl$_2$, c) Et$_3$N / DMAP, d) H$_2$ / Pd(OH)$_2$ / C

Scheme IXA provides a synthesis scheme for producing intermediate GFE carboxylic acids including the use of 4-bromobenzoic acids as starting material. For example a 4-bromobenzoic acid can be esterified by treatment with carbonyldiimidazole followed by an alcohol such as tert-butanol. The ester is treated with n-butyl lithium followed by an addition of N, N-dimethyl formamide to give the aldehyde ester, or by addition of carbon dioxide to give the acid ester, which is converted to the acid chloride ester with oxalyl chloride. The ester can also be reacted with n-butyl lithium and a benzaldehyde to give the diphenyl carbinol, which is oxidized with, for example, chromic acid, and deprotected to provide GFE carboxylic acids. The ester can be reacted with n-butyl lithium and benzoyl chloride to give the diphenyl ketone, which is deprotected to also provide GFE carboxylic acids.

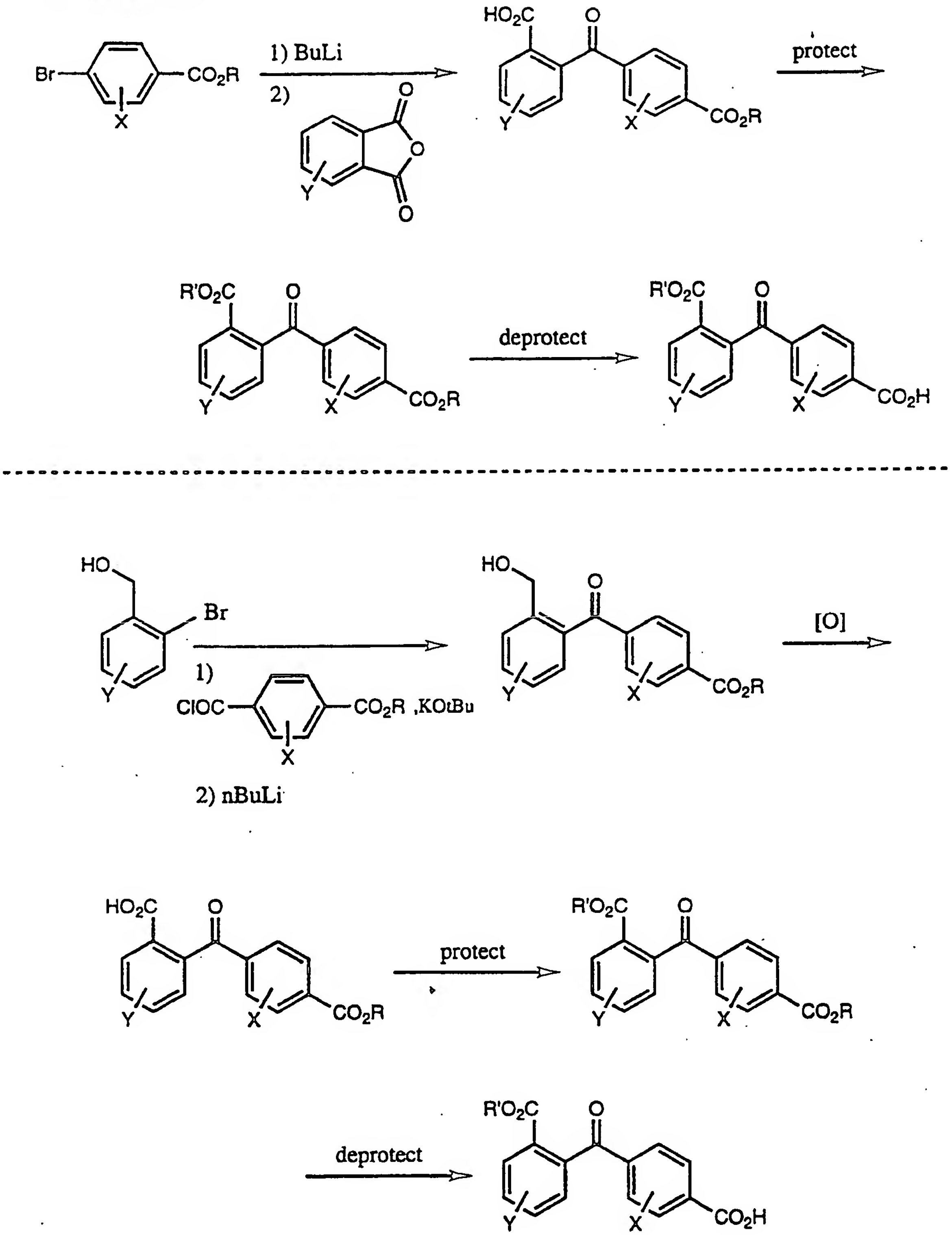
Scheme IX A



1) CDI
2) ROH
1) n-BuLi
2) DMF
1) n-BuLi
2) CO2
(COCl)2
1) BuLi
2)
[O]
deprotect
1) BuLi
2)
deprotect

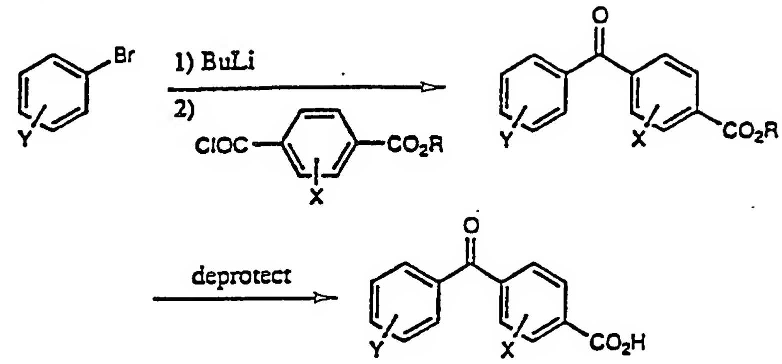
Scheme IXB provides a synthesis scheme for producing intermediate GFE carboxylic acids including the use of either 4-bromobenzoic esters from scheme IXA or benzyl alcohols as starting material. For example, a 4-bromobenzoic ester can be treated with n-butyl lithium and phthalic anhydride to afford the 2'-carboxybenzophenone ester, which is protected with, for example, benzyl alcohol esterification at the 2' position and deprotected at the other ester position to provide GFE carboxylic acids. In an alternative, preferred method, the alcohol is coupled with the acid chloride and treated with one equivalent of nBuLi which provides, upon rearrangement, the hydroxy ketone. Oxidation to the acid is effected in a two-step process using first pyridinium dichromate (PDC) or TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) followed by tetrabutylammonium permanganate (nBu_4MnO_4) or sulfamic acid (NH_2SO_3H) and sodium chlorite ($NaClO_2$). The resultant acid is protected, for example, by conversion to the benzyl ester and then deprotected at the other ester position to provide the family of GFE carboxylic acids.

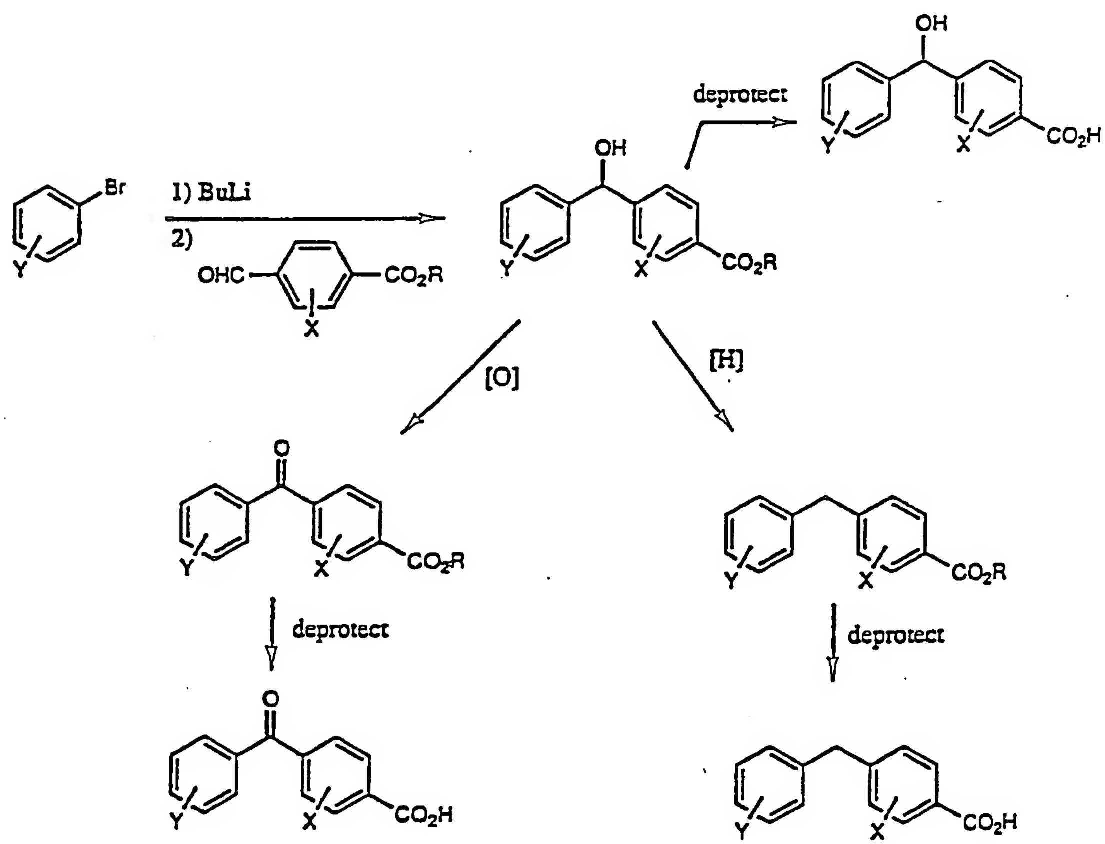
Scheme IX B


1) BuLi
2)
protect
deprotect
[O]
1)
2) nBuLi
,KOtBu
protect
deprotect

Scheme IXC provides a synthesis scheme for producing GFE carboxylic acids including the use of bromobenzenes as starting material. For example, a bromobenzene can be treated with n-butyl lithium and the acid chloride ester from scheme IXA to afford the benzophenone ester, which is deprotected to provide GFE carboxylic acids. The bromobenzene can also be treated with n-butyl lithium and the aldehyde ester from scheme IXA to give the diphenylcarbinol ester, which is either deprotected directly, oxidized with, for example, chromic acid and deprotected, or reduced with, for example, hydrogen and deprotected to provide the family of GFE carboxylic acids.

Scheme IX C

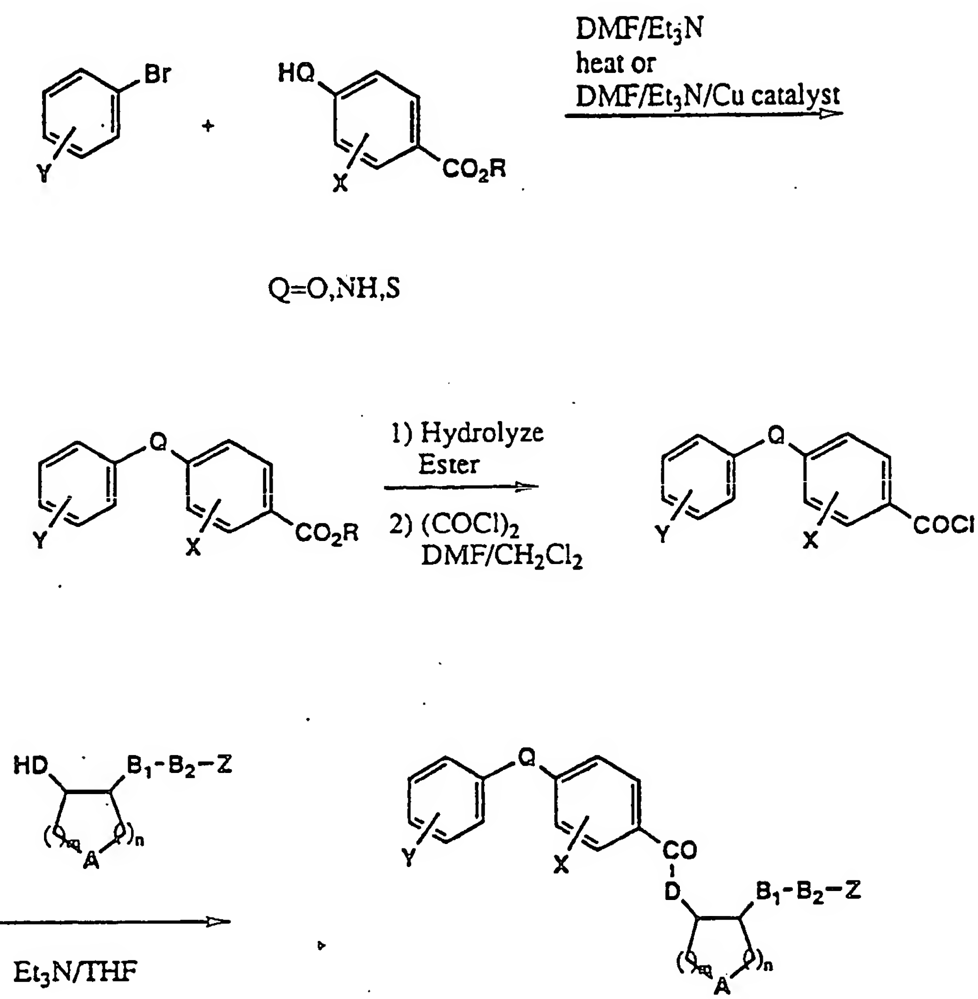

Br
1) BuLi
2)
ClOC
CO2R
X
Y
O
CO2R
deprotect
CO2H


Br
1) BuLi
2)
OHC
CO2R
X
Y
OH
deprotect
CO2H
[O]
[H]
O
deprotect
deprotect

Scheme IXD provides a synthesis scheme for producing compounds according to the present invention including the use of halobenzenes, for example, bromobenzenes, and heterocyclic or cyclic compounds substituted with B_1-B_2-Z and DH, which are described in other schemes, as starting materials. For example, a bromobenzene can be reacted with a 4-heterobenzoate ester, in dimethyl formamide/triethylamine with heat or copper catalyst to give GFE acid chloride. This can be treated with heterocyclic compounds substituted with B_1-B_2-Z and DH in the presence of tetrahydrofuran/triethylamine to provide this family of balanoids.

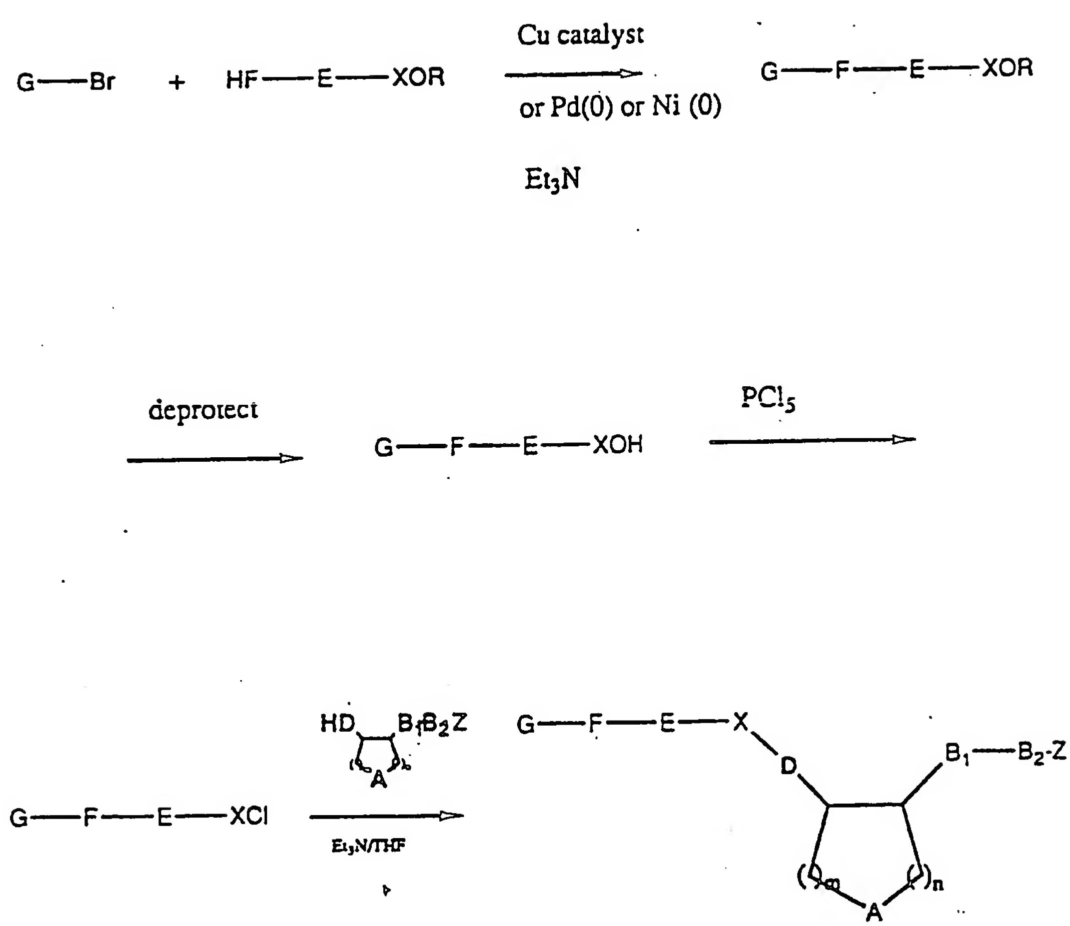
Scheme IX D

Arm 1 synthesis (continued):



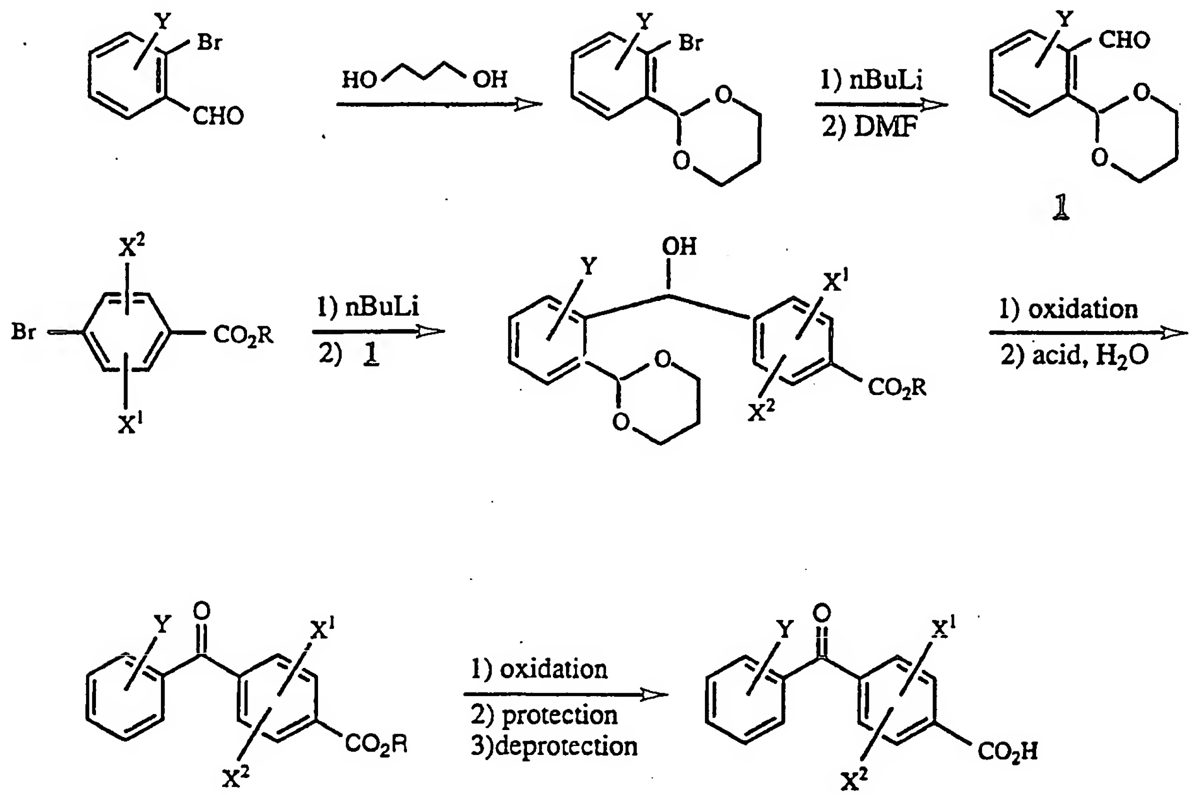
Scheme IXE provides a synthesis scheme for producing compounds according to the present invention including the use of aromatic or heteroaromatic halides protected, hetero-substituted aryl or heteroaryl acids or alcohols, and heterocyclic or cyclic compounds substituted with B_1-B_2-X and DH, which are described in other schemes, as starting materials. For example, a bromoaromatic can be reacted with a protected 4-hetero-substituted aryl acid or alcohol in the presence of transition metal catalyst, for example, copper, and base to afford protected GFE acid or alcohol, which can be deprotected and treated with, for example, phosphorous penta chlorides to provide GFEX chloride. This is reacted with heterocyclic or cyclic compounds substituted with B_1-B_2-Z and DH to provide another family of balanoids.

Scheme IX E


G—Br + HF—E—XOR
Cu catalyst
or Pd(0) or Ni (0)
Et3N
G—F—E—XOR
deprotect
G—F—E—XOH
PCl5
G—F—E—XCl
HD B1B2Z
A
Et3N/THF
G—F—E—X
D
B1—B2-Z
( )m
( )n
A

Scheme IX F provides a preferred method for the preparation of the GFE-CO_2H. Intermediate aldehyde is first protected, for example, as a cyclic acetal, which is then treated with nBuLi and DMF to afford aldehyde 1. Aryl bromide, is treated with n-butyl lithium and then aldehyde 1 to afford the alcohol. Oxidation using, for example MnO_2 followed by acidic hydrolysis of the acetal gives the ketoaldehyde. Oxidation to the acid using, for example, sodium chlorite and sulfamic acid, followed by the appropriate deprotection sequences affords GFE-CO_2H.

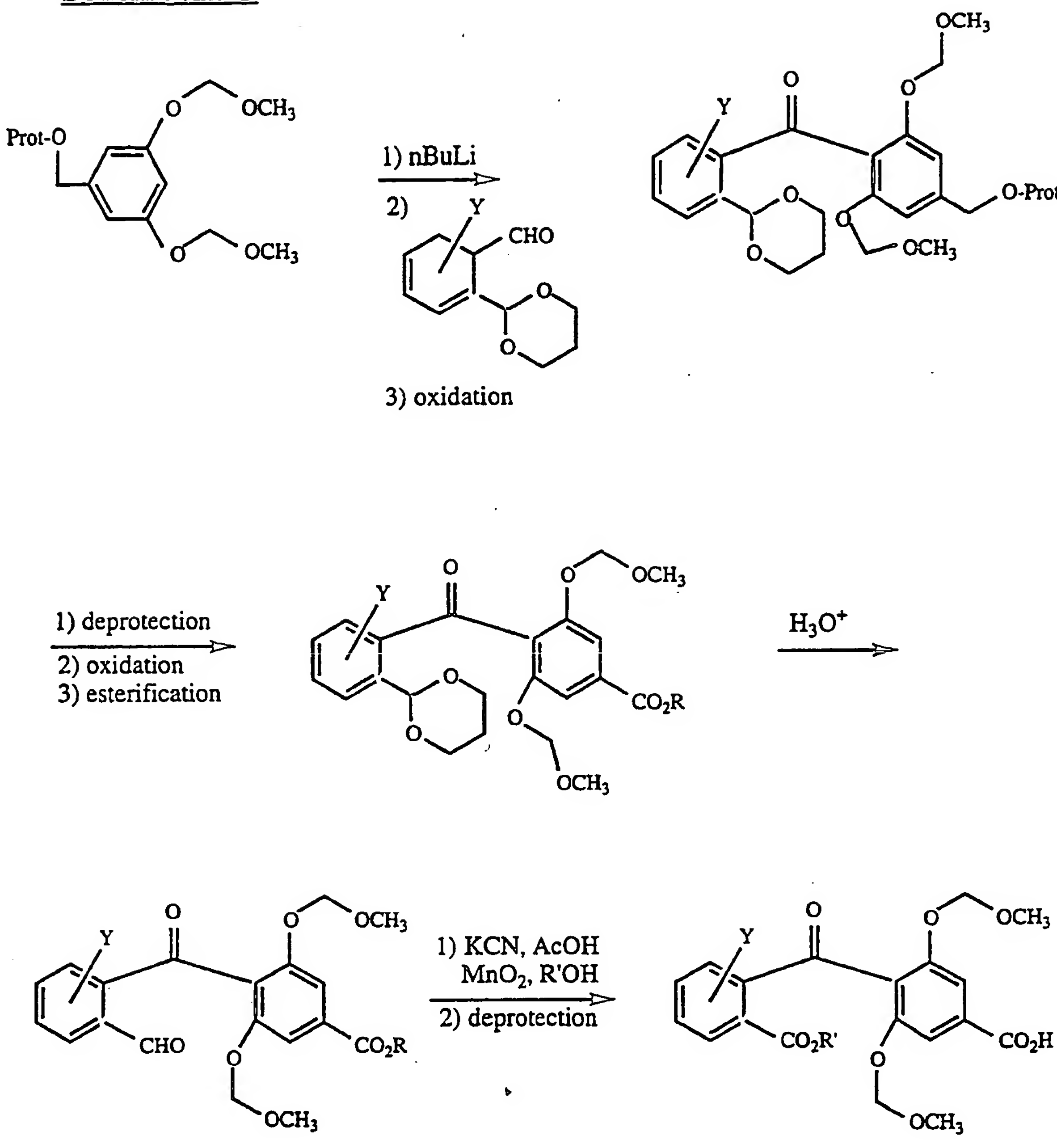
Scheme IX F


Y
Br
CHO
HO OH
Y
Br
O
O
1) nBuLi
2) DMF
Y
CHO
O
O
1
X²
Br
CO₂R
X¹
1) nBuLi
2) 1
OH
Y
X¹
O
O
X²
CO₂R
1) oxidation
2) acid, H₂O
Y
O
X¹
CO₂R
X²
1) oxidation
2) protection
3)deprotection
Y
O
X¹
CO₂H
X²

Scheme IX G describes a preferred method for the preparation of GFE-CO_2H where E is substituted with two OH or OR groups. Protected bis-phenol is treated with n-butyl lithium followed by aldehyde (prepared in Scheme IX F) provides, after oxidation with, for example, MnO_2 the ketone intermediate. Following deprotection, the primary alcohol is oxidized, using, for example MnO_2 followed by sodium chlorite/hydrogen peroxide. Hydrolysis of the acetal followed by treatment with MnO_2, KCN, acetic acid and the alcohol R'-OH provides the desired GFE-CO_2H.

A detailed scheme for benzophenone synthesis is shown in Scheme IX H.

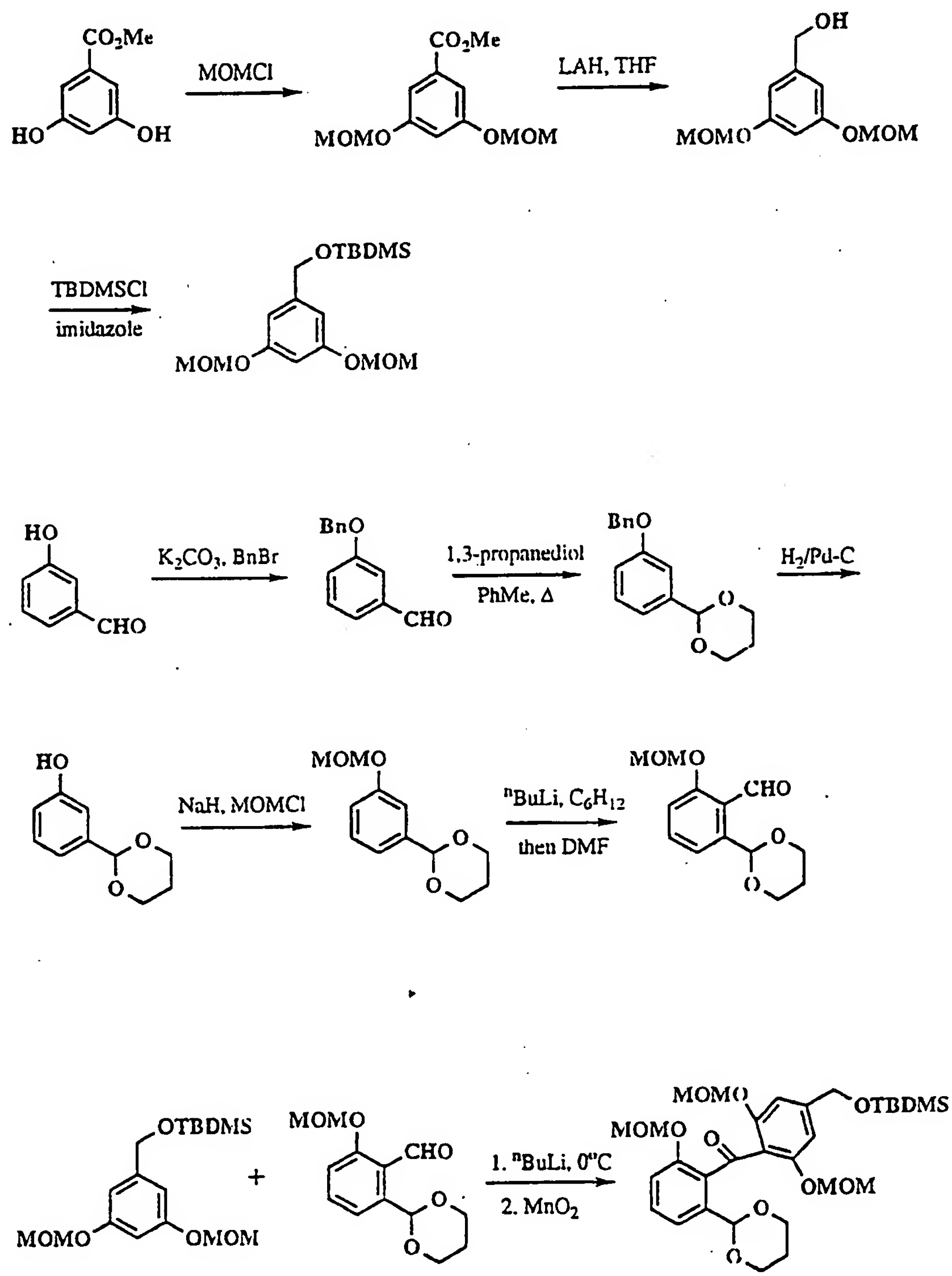
Scheme IX G

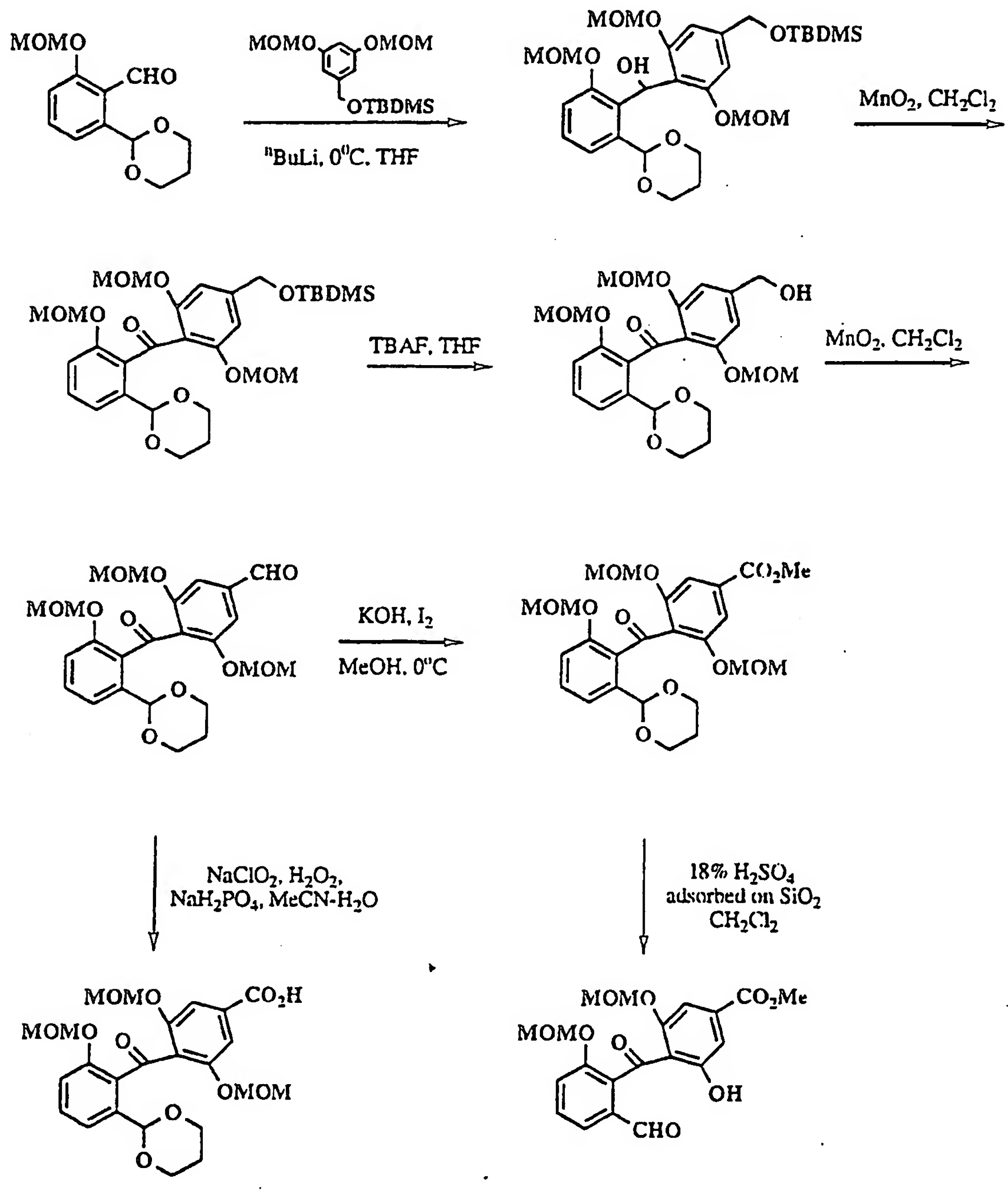


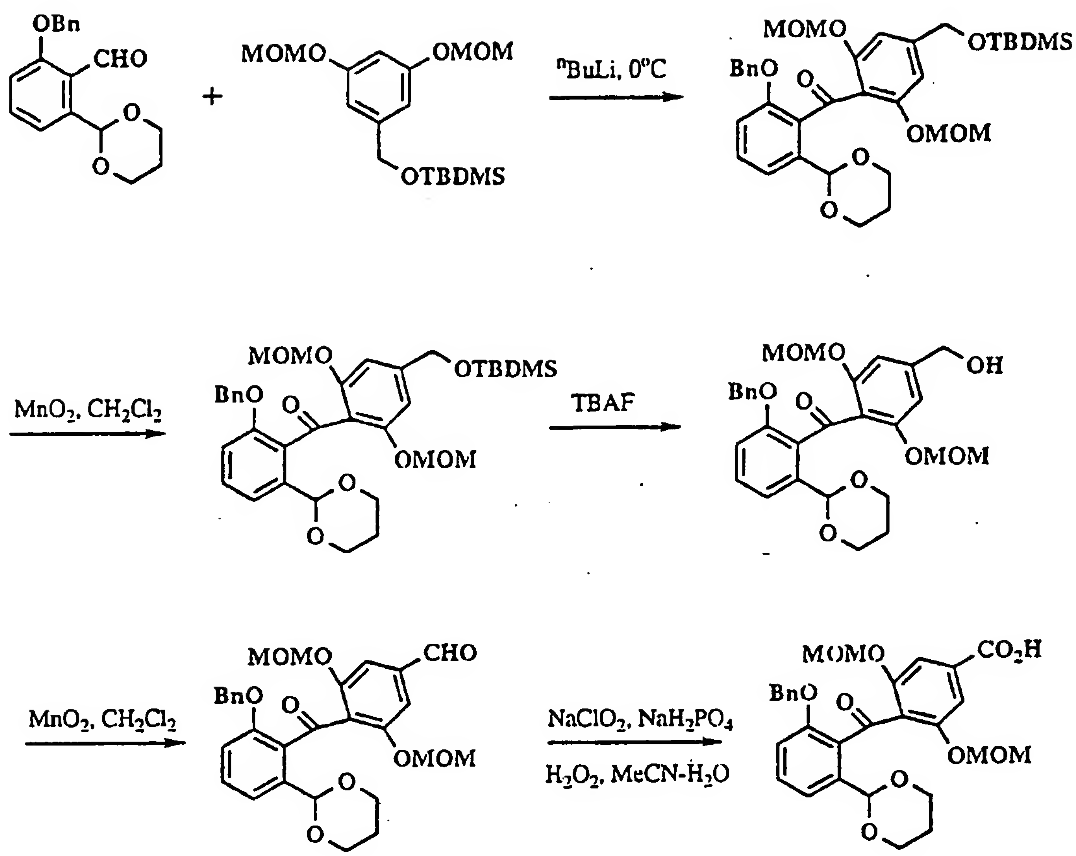
Prot-O
OCH3
1) nBuLi
2)
Y
CHO
3) oxidation
O-Prot
1) deprotection
2) oxidation
3) esterification
CO2R
H3O+
1) KCN, AcOH
MnO2, R'OH
2) deprotection
CO2R'
CO2H

Scheme IX H

Synthesis of MOM-Protected Benzophenone

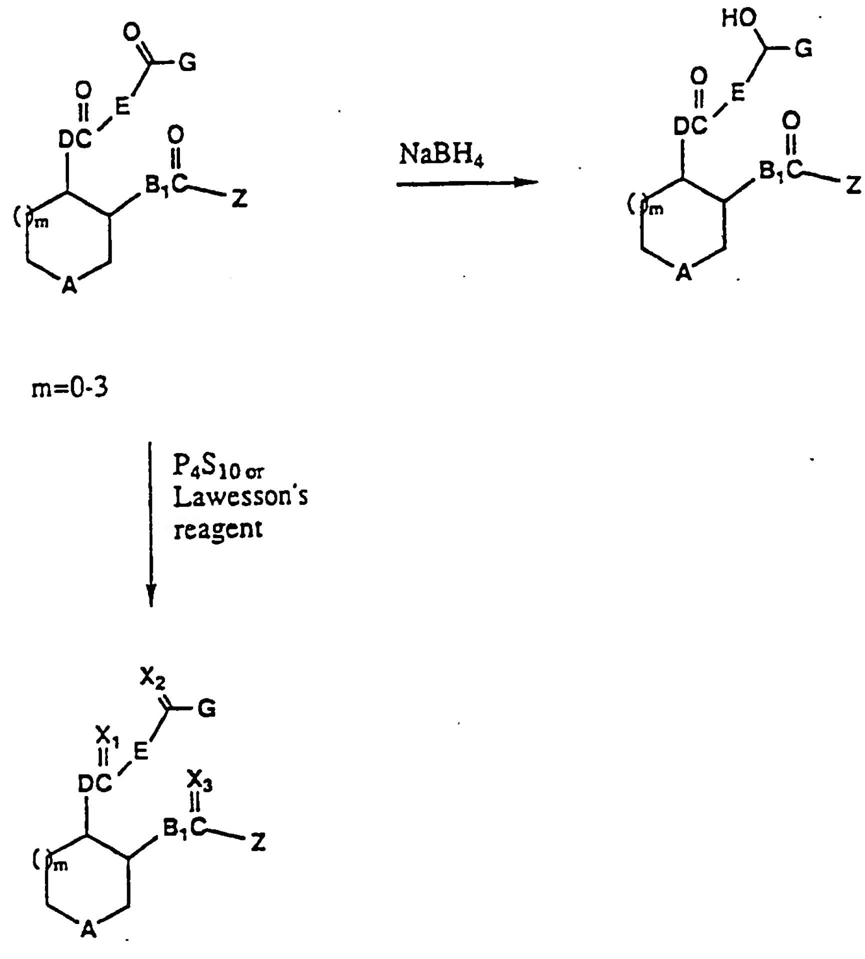



MOMO
CHO
MOMO
OMOM
OTBDMS
$^{n}BuLi, 0^{0}C, THF$
MOMO
MOMO
OH
OTBDMS
OMOM
MnO_2, CH_2Cl_2
MOMO
MOMO
OTBDMS
OMOM
TBAF, THF
MOMO
MOMO
OH
OMOM
MnO_2, CH_2Cl_2
MOMO
MOMO
CHO
OMOM
KOH, I_2
MeOH, 0°C
MOMO
MOMO
CO_2Me
OMOM
$NaClO_2, H_2O_2,$
$NaH_2PO_4, MeCN-H_2O$
18% H_2SO_4
adsorbed on SiO_2
CH_2Cl_2
MOMO
MOMO
CO_2H
OMOM
MOMO
MOMO
CO_2Me
OH
CHO


OBn
CHO
MOMO
OMOM
OTBDMS
nBuLi, 0°C
BnO
MnO2, CH2Cl2
TBAF
OH
CHO
NaClO2, NaH2PO4
H2O2, MeCN-H2O
CO2H

Scheme X provides means for producing compounds according to the present invention including the use of heterocyclic or cyclic compounds substituted with B_1-B_2-Z and DXEFG where F is C=O, which are described in other schemes, as starting materials. For example, a heterocyclic or cyclic compound substituted with B_1-B_2-Z and DXEFG where F is C=O can be treated with a reducing agent such as sodium borohydride to afford balanoids where F is CHOH, or it can be treated with a sulfurizing agent, for example, phosphorus pentasulfide, to provide the family of balanoids with B_2 and/or F equal to C=S.

Scheme X



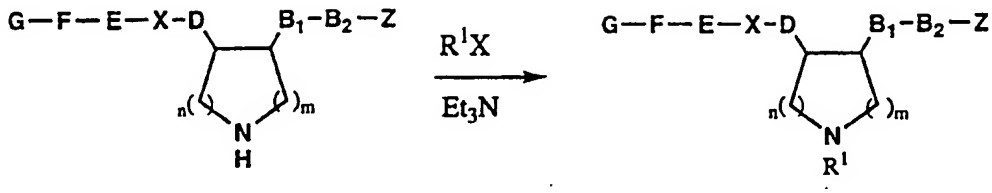
m=0-3

X_1,X_2,X_3 independently = O or S

Scheme XIA provides a synthesis scheme for producing compounds according to the present invention including the use of heterocyclic compounds substituted with B_1-B_2-Z and DXEFG where A is NH, described in other schemes, as starting materials. For example, a heterocyclic compound substituted with B_1-B_2-Z and DXEFG where A is NH can be treated with an alkylating agent, sulfonylating agent, or acylating agent, for example acetyl chloride, in the presence of base to provide the family of balanoids with a substanted nitrogen.

In an alternative approach, Scheme XI B, the R^1 group can be appended at an earlier stage in the synthesis using appropriately protected intermediates. For example, heterocyclic intermediate can be treated with an alkylating agent, sulfonylating agent or acylating agent, in the presence of base to provide the intermediate where R^1 is not hydrogen.

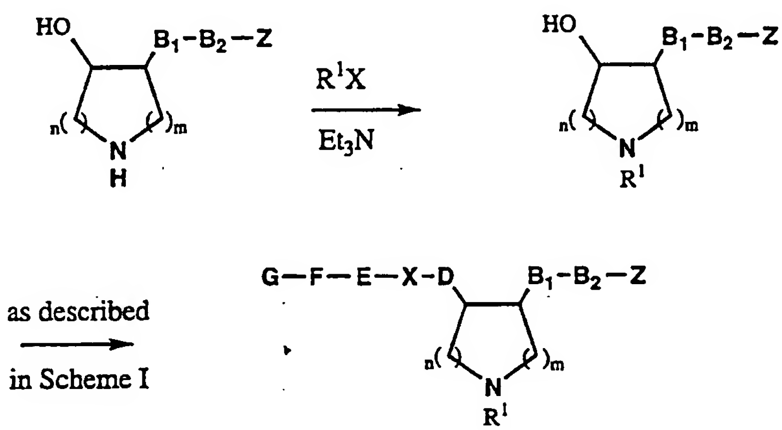
Scheme XI A



m=1-4,n=1-4
m+n<or=5

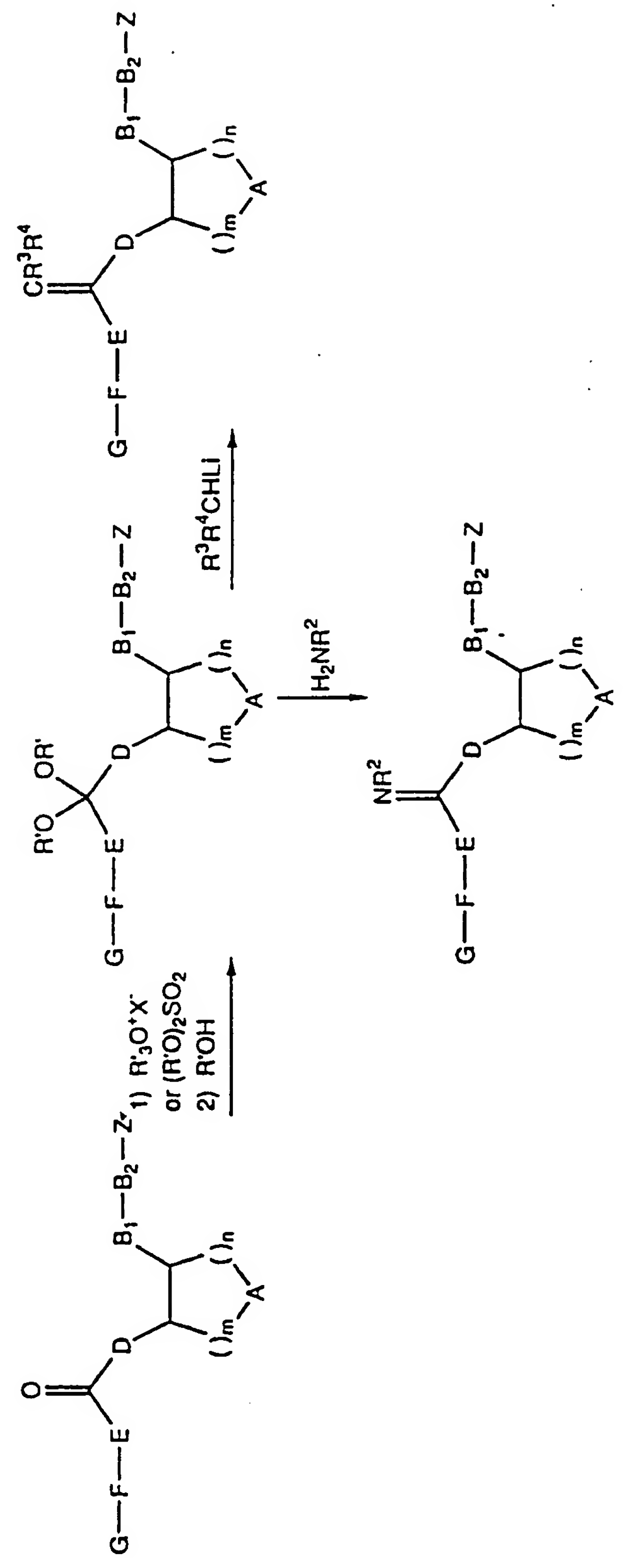
R^1=lower alkyl, aryl, or JR^2 where J=CO,CN, or SO_2 and R^2=lower alkyl, aryl, alkylamino, or alkoxy

Scheme XI B



Scheme XII provides a synthesis scheme for producing compounds according to the present invention including the use of cyclic or heterocyclic compounds substituted with B_1-B_2-Z and DXEFG where X is C=O, which are described in other schemes, as starting materials. For example, a heterocyclic compound substituted with B_1-B_2-Z and DXEFG where is C=O can be treated with an alkylating agent, for example dimethyl sulfate and an alcohol, such as methanol, to give the intermediate ketal. This can be reacted with an organometallic, for example, the lithium salt of diethyl malonate, to provide the family of balanoids in which x is $C=CR^3R^4$. The ketal can be reacted with a primary amine, for example, butylamine, to provide the family of balanoids in which X is $C=NR^2$.

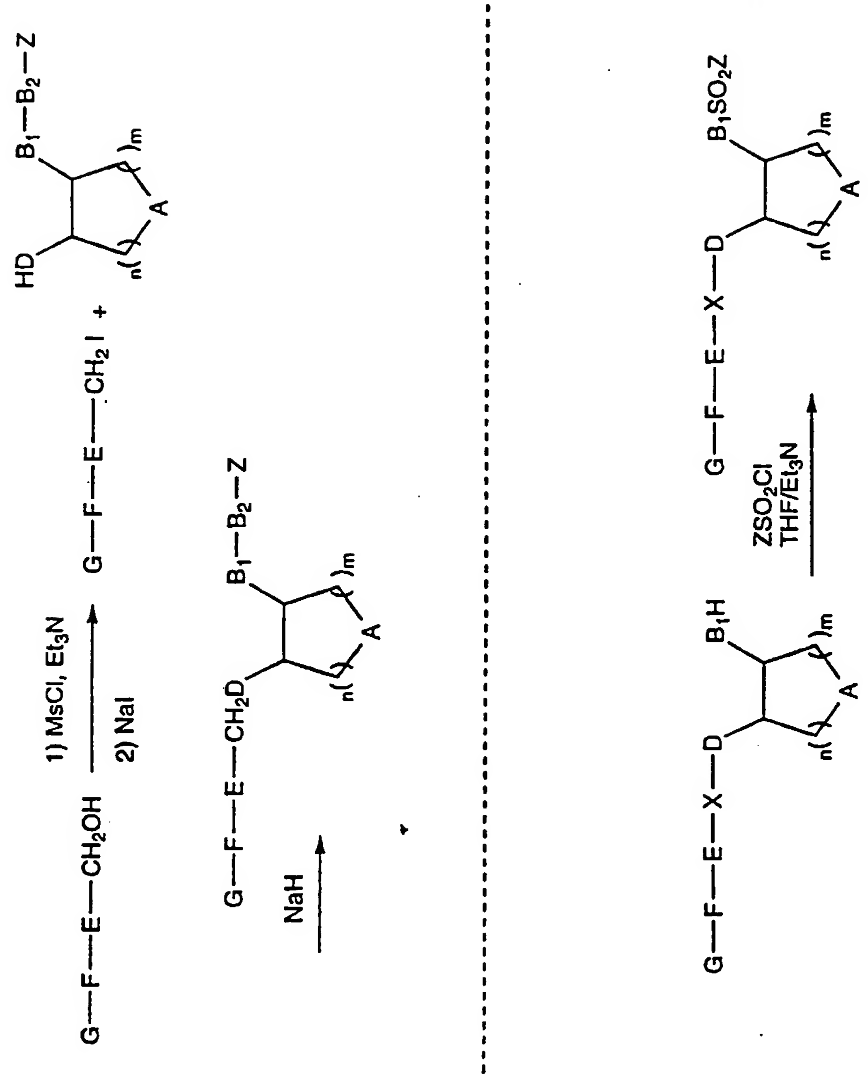
Scheme XII



Scheme XIII provides syntheses for producing compounds according to the present invention including the use of GFE carboxylic acids and cyclic or heterocyclic compounds substituted with B_1-B_2-Z and DH or B,H and DXEFG, which are described in other schemes, as starting materials. For example, a GFE carbinol can be treated with mesyl chloride and an amine base, such as triethylamine, followed by treatment with an iodide source such as sodium iodide to afford a GFE methyl iodide. This can be reacted with a cyclic or heterocyclic compound substituted with B_1-B_2-Z and DH in the presence of base such as sodium hydride to provide the family of balanoids in which X is CH_2.

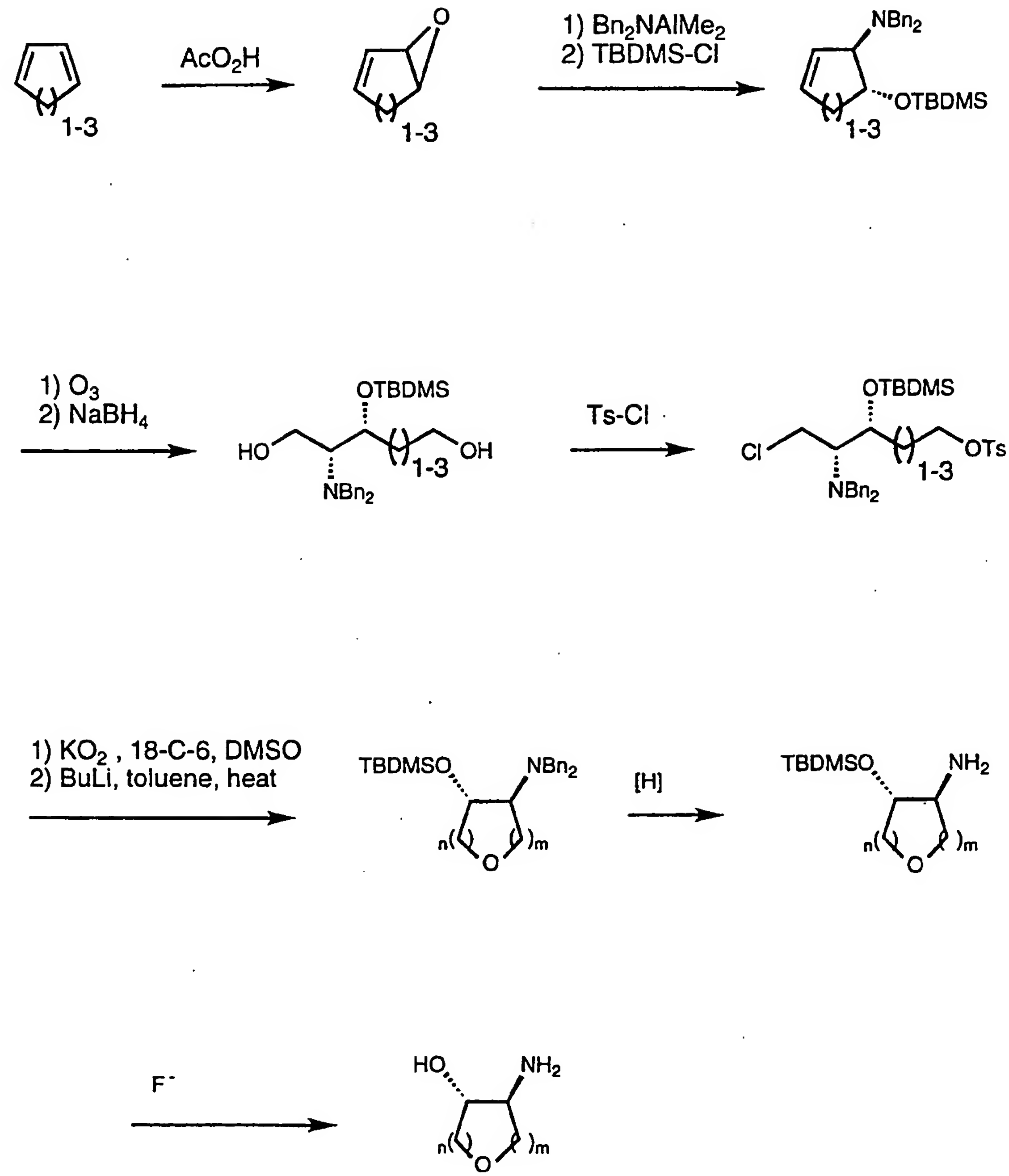
The cyclic or heterocyclic compound substituted with B,H and DXEFG can be reacted with a Z sulfonyl chloride, for example, benzenesulfonyl chloride, in the presence of base to provide the family of balanoids in which B_2 is SO_2.

Scheme XIII



Scheme XIV A provides a synthesis scheme for producing intermediates which are heterocyclic compounds substituted with B_1=NH_2 and D=OH and in which A is oxygen. For example, a cyclic diene such as cyclopentadiene can be treated with a peracid such as peracetic acid and the epoxide opened with an amino species, for example, (dibenzylamino) dimethyl aluminum, followed by butyldimethylsilyl chloride to obtain the protected amino alcohol. This can be ozonolyzed and reduced to the diol, which is treated with tosyl chloride to give the chloro tosylate. Treatment with bis(trimethyltin)oxide or preferably potassium superoxide and a crown ether, for example, 18-C-6, provides the chloroalcohol which is ring closed on treatment with a strong base, such as methyllithium or butyllithium to afford the protected heterocyclic compound, which is deprotected to heterocyclic compounds substituted with B_1=NH_2 and D=OH and in which A is oxygen.

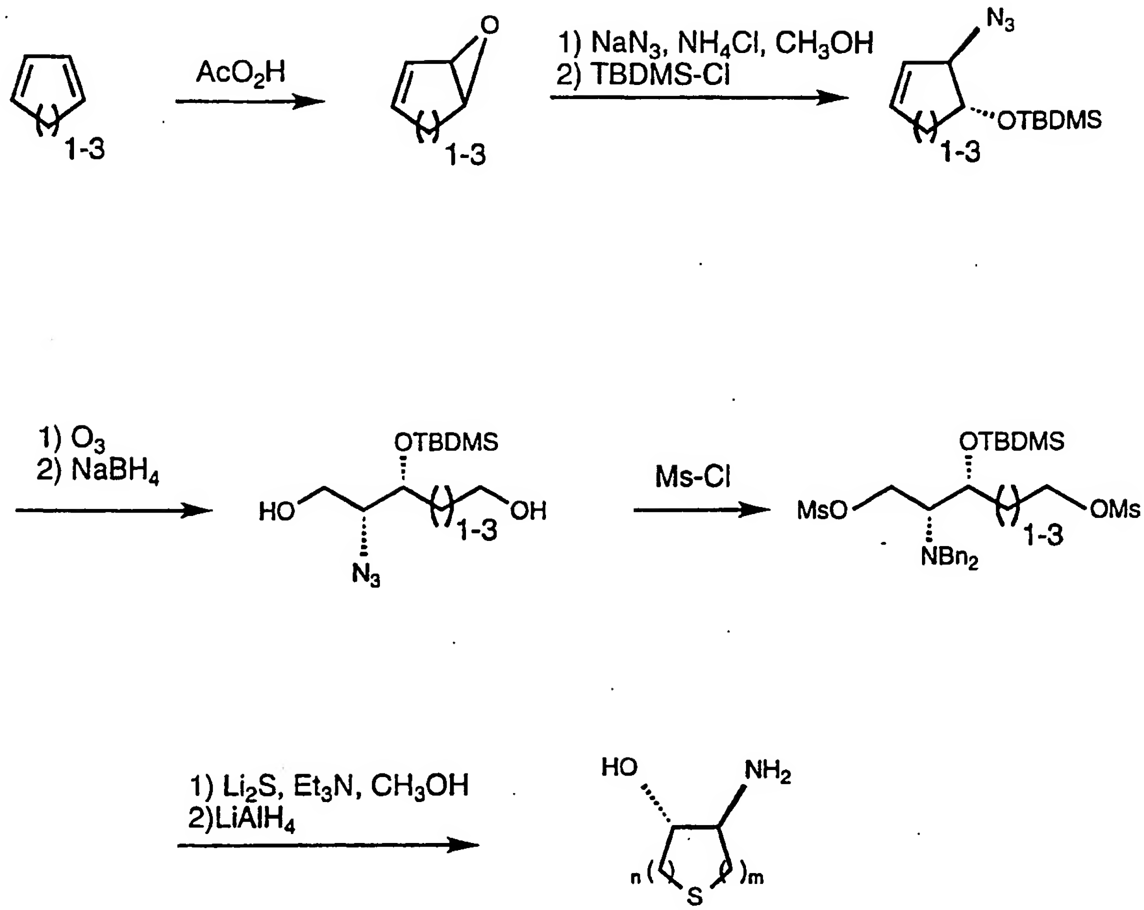
Scheme XIV A


AcO2H
1) Bn2NAlMe2
2) TBDMS-Cl
NBn2
OTBDMS
1-3
1) O3
2) NaBH4
OTBDMS
HO
OH
NBn2
Ts-Cl
Cl
OTs
1) KO2 , 18-C-6, DMSO
2) BuLi, toluene, heat
TBDMSO
NBn2
[H]
NH2
n
m
O
F-
HO

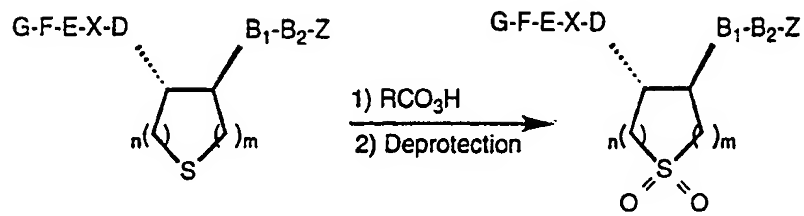
Scheme XIV B provides a synthesis scheme for producing intermediates which are heterocyclic compounds substituted with $B_1=NH_2$ and D=OH and in which A is sulfur. For example, a cyclic diene such as cyclopentadiene can be treated with a peracid such as peracetic acid and the epoxide opened with an azide species, for example, sodium azide, followed by t-butyldimethylsilyl chloride to obtain the protected amino alcohol. This can be ozonolyzed and reduced to the diol, which is treated with mesyl chloride to give the dimesylate and ring closed with, for example, bis(trimethyltin) sulfide or preferably, lithium sulfide and an amine base such as triethylamine. Reduction of the azide and deprotection occurs on treatment with lithium aluminum hydride to give heterocyclic compounds substituted with $B_1 = NH_2$ and D = OH and in which A is sulfur.

Compounds where A is SO_2 can be prepared from compounds where A is sulfur by treatment with an oxidizing agent, for example, peracetic acid,followed by deprotection to provide compounds wherein A is SO_2 (Scheme XIV C).

Scheme XIV B

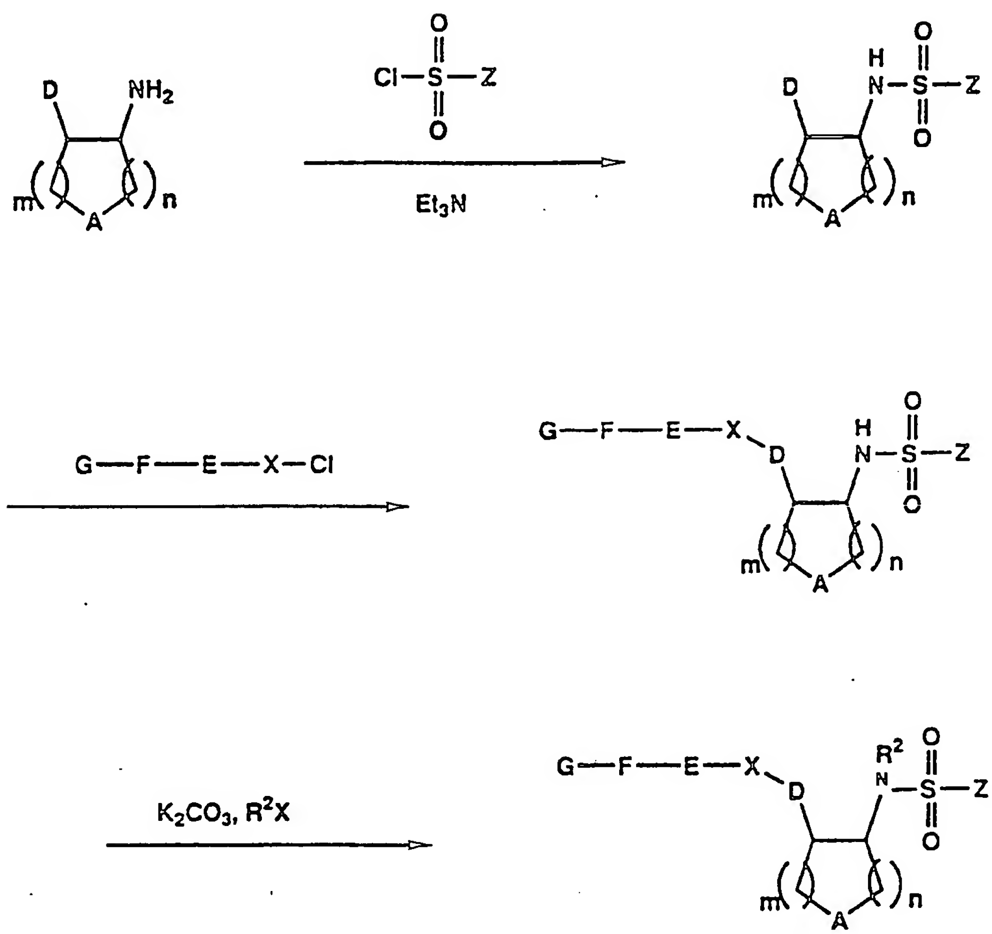

AcO2H
1) NaN3, NH4Cl, CH3OH
2) TBDMS-Cl
1-3
O
N3
OTBDMS
1) O3
2) NaBH4
HO
OH
Ms-Cl
MsO
OMs
NBn2
1) Li2S, Et3N, CH3OH
2)LiAlH4
NH2
S
n
m

Scheme XIV C



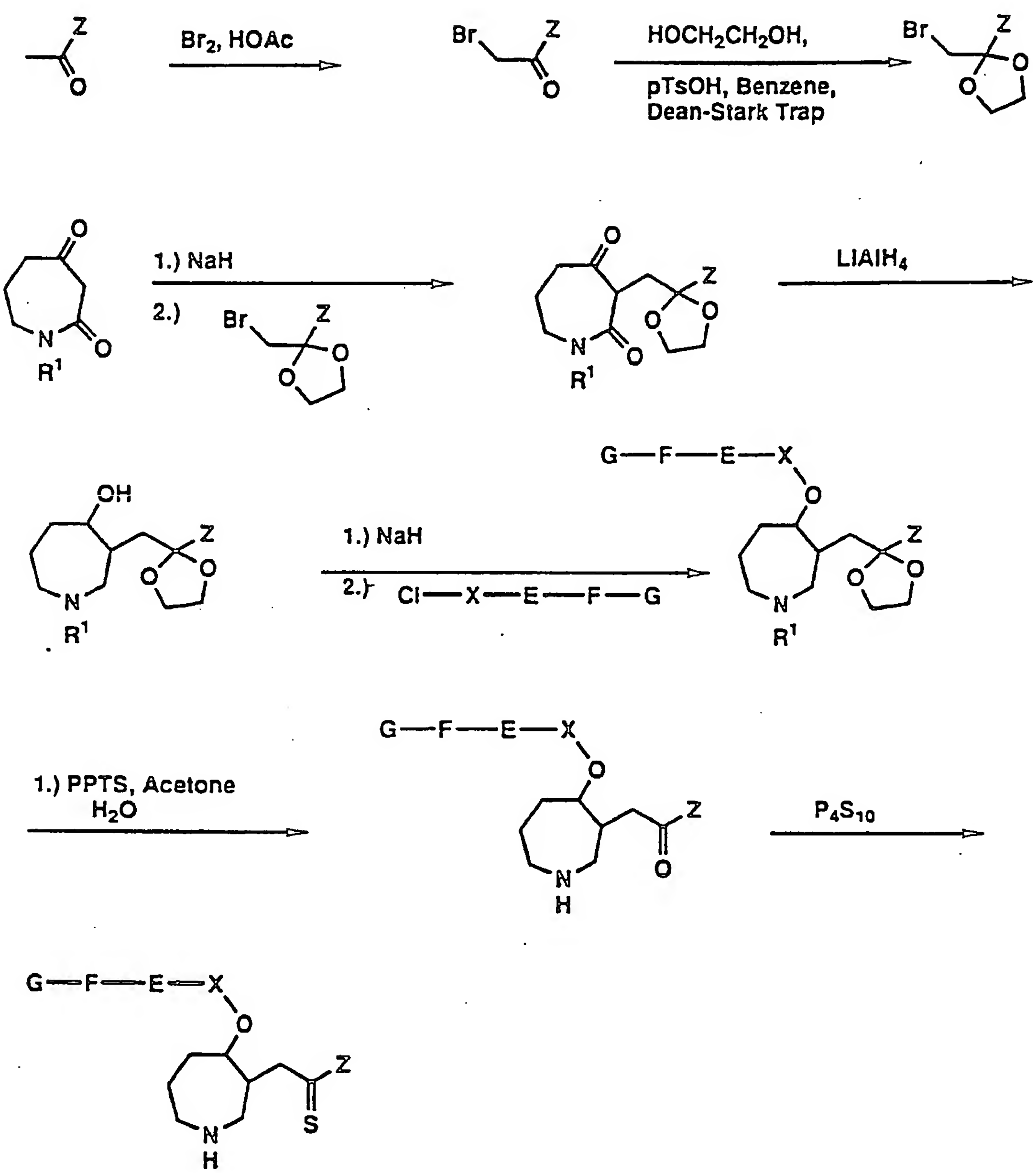
Scheme XV provides a synthesis scheme for producing compounds according to the present invention including the use of Z sulfonyl chlorides, such as benzenesulfonyl chloride, and cyclic or heterocyclic compounds substituted with B_1=NH_2 and DH, which are described in other schemes, as starting materials. For example, a Z sulfonyl chloride and a cyclic or heterocyclic compound substituted with B_1=NH_2 and DH are combined in the presence of base to afford the sulfonamide, which is reacted with GFEX halide to provide the family of balanoids in which B_1 is N and B_2 is SO_2.

Scheme XV



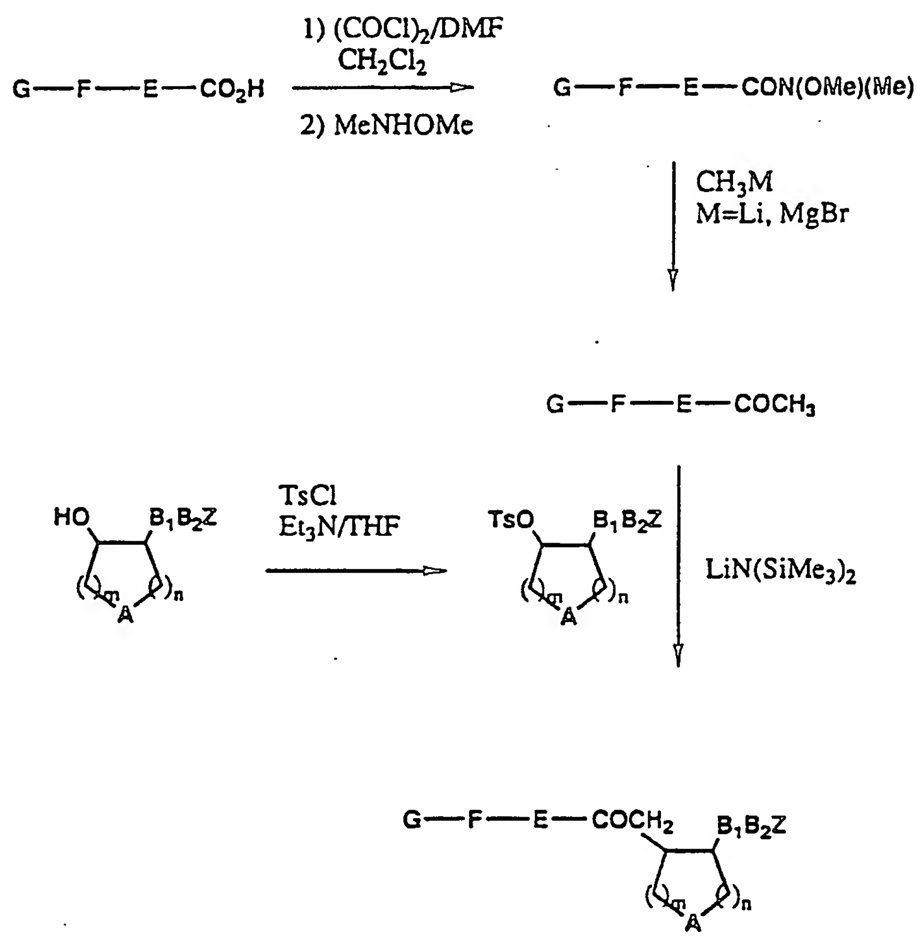
Scheme XVI provides a synthesis scheme for producing compounds according to the present invention including the use of ketones, for example, acetophenone, and azepinediones, such as 1-benzylazepin-2,4-dione, as starting materials. For example, the ketone can be brominated with bromine in acetic acid and protected with ethylene glycol to afford the bromomethyl ketal, which is added to a base-treated solution of the azepinedione to give the alkylated azepinedione. This is reduced to the hydroxyazepine with, for example, lithium aluminum hydride, and reacted with base and GFEX halide, which is described in other schemes, then deprotected to provide the family of balanoids where B_1 is CH_2, B_2 is C=O, and D is O. These compounds can be reacted with, for example, phosphorus tetrasulfide, to provide the family of balanoids where B_1 is CH_2, B is C=S and D is O.

Scheme XVI


Br$_2$, HOAc
HOCH$_2$CH$_2$OH,
pTsOH, Benzene,
Dean-Stark Trap
1.) NaH
2.)
LiAlH$_4$
1.) NaH
2.) Cl—X—E—F—G
1.) PPTS, Acetone
H$_2$O
P$_4$S$_{10}$

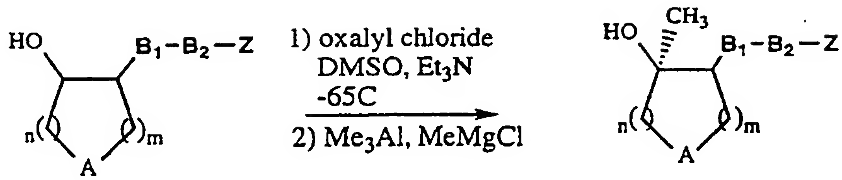
Scheme XVII provides a synthesis scheme for producing compounds according to the present invention including GFE carboxylic acids, which are described in other schemes, and cyclic or heterocyclic groups substituted with OH and B_1B_2Z, also described in other schemes, as starting materials. For example, a GFE carboxylic acid can be treated with oxalyl chloride and N,O-dimethylhydroxylamine to afford the methoxymethyl amide, which is reacted with a methyl organometallic to give the methyl ketone. This is then deprotonated with base and reacted with the product from treatment of a cyclic or heterocyclic group substituted with DH and B_1B_2z with tosyl chloride to provide the family of balanoids with D as CH_2 and X as C=O.

Scheme XVII


G—F—E—CO_2H
1) $(COCl)_2$/DMF
CH_2Cl_2
2) MeNHOMe
G—F—E—CON(OMe)(Me)
CH_3M
M=Li, MgBr
G—F—E—$COCH_3$
HO
B_1B_2Z
TsCl
Et_3N/THF
TsO
B_1B_2Z
$LiN(SiMe_3)_2$
G—F—E—$COCH_2$
B_1B_2Z
A
m
n

Scheme XVIII provides a synthetic scheme for compounds of the invention where K is not equal to H. Oxidation of the alcohol using, for example, oxalyl chloride and dimethylsulfoxide (Swern oxidation) followed by addition of an organometallic reagent, for example, the complex of trimethylaluminum and methyl magnesium chloride to afford the tertiary alcohol. This intermediate is converted using the Scheme I to compounds of the invention.

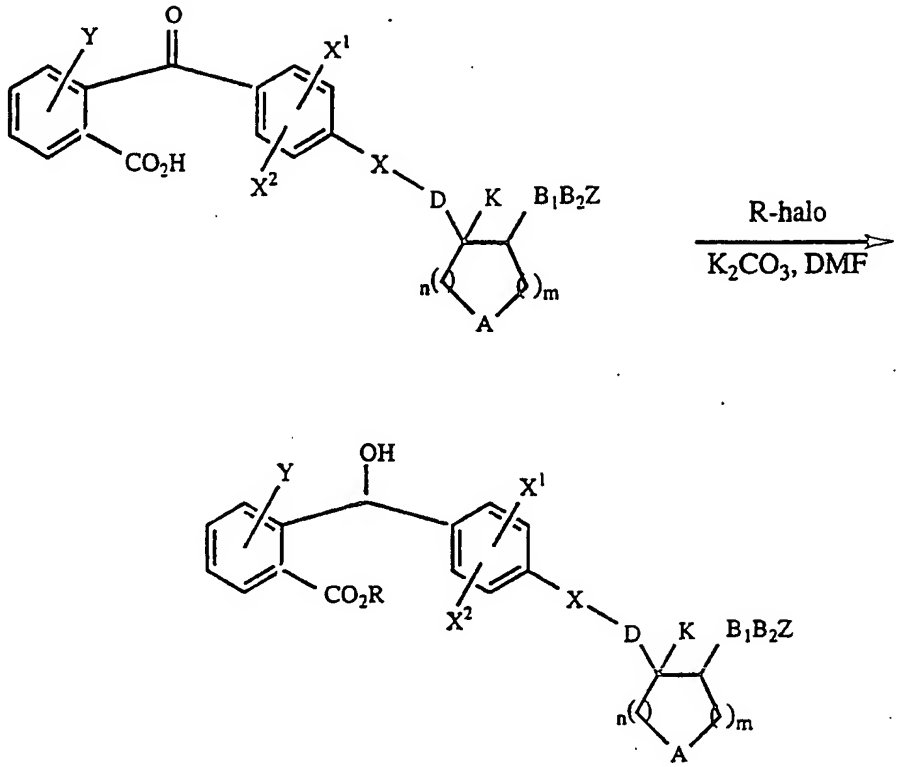
Scheme XVIII



$\xrightarrow[\text{in Scheme I}]{\text{as described}}$ Targets where $K = CH_3$

Scheme XIX provides a synthetic scheme for compounds of the invention where the group G is substituted with an alkoxycarbonyl group. Compounds wherein G is substituted with a carboxy group are treated with an alkylating agent, for example, methyl iodide, and a base such as sodium carbonate to provide the target compounds.

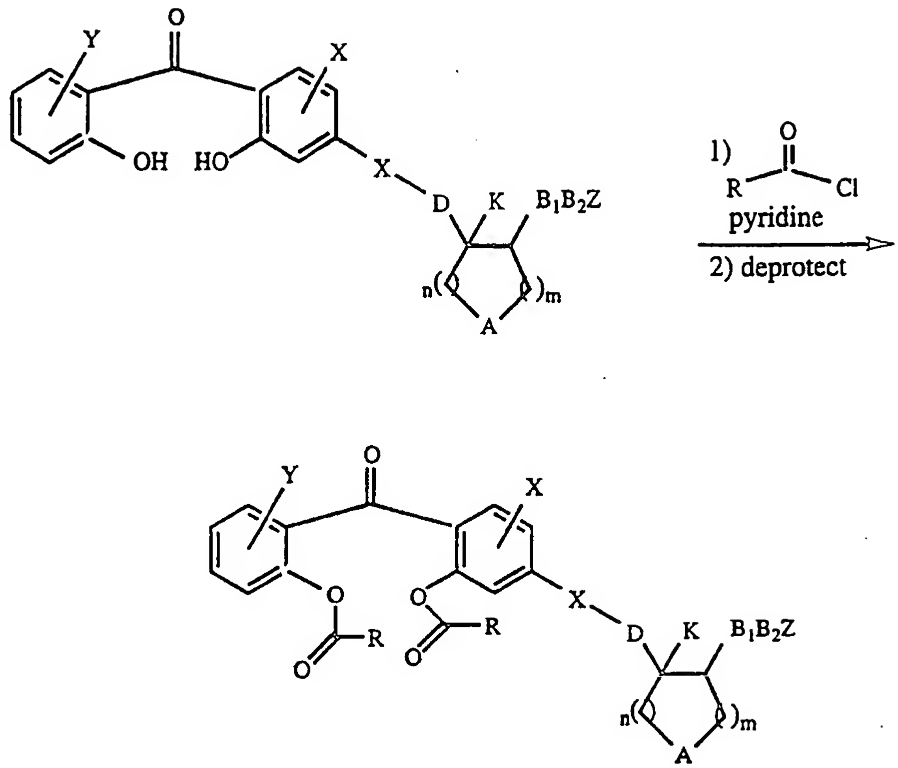
Scheme XIX



where R = alkyl, substituted alkyl

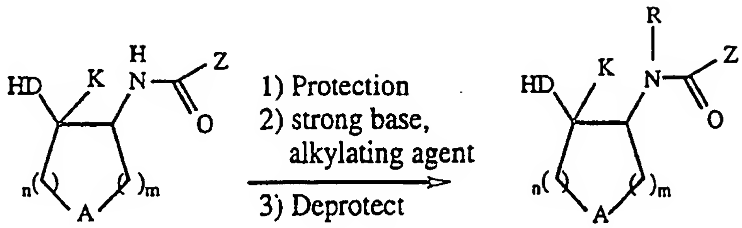
Scheme XX provides a synthetic route for compounds of the invention where G and/or E residues are substituted with acyloxy groups. Target compounds, which possess one or more hydroxyl groups on G or E is treated with an acylating agent, for example, acetyl chloride, ethyl chloroformate, and the like, in the presence of a base such as pyridine or triethylamine to provide the target compounds.

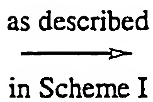
Scheme XX


Y
O
X
OH
HO
X
D
K
B_1B_2Z
n
m
A
1)
O
R
Cl
pyridine
2) deprotect
Y
O
X
O
O
R
O
O
R
X
D
K
B_1B_2Z
n
m
A

Scheme XXI provides a synthetic scheme for the preparations of compounds where B_1 is N-R and B_2 is C=O. Intermediate amide, following protection of the D functionality, is treated with a strong base such as KOtBu or KH and an alkylating agent such as methyliodide or dimethylsulfate to provide the intermediate where B_1 is N-R. This can be converted using the procedures outlined in Scheme I to afford the target compound.

Scheme XXI

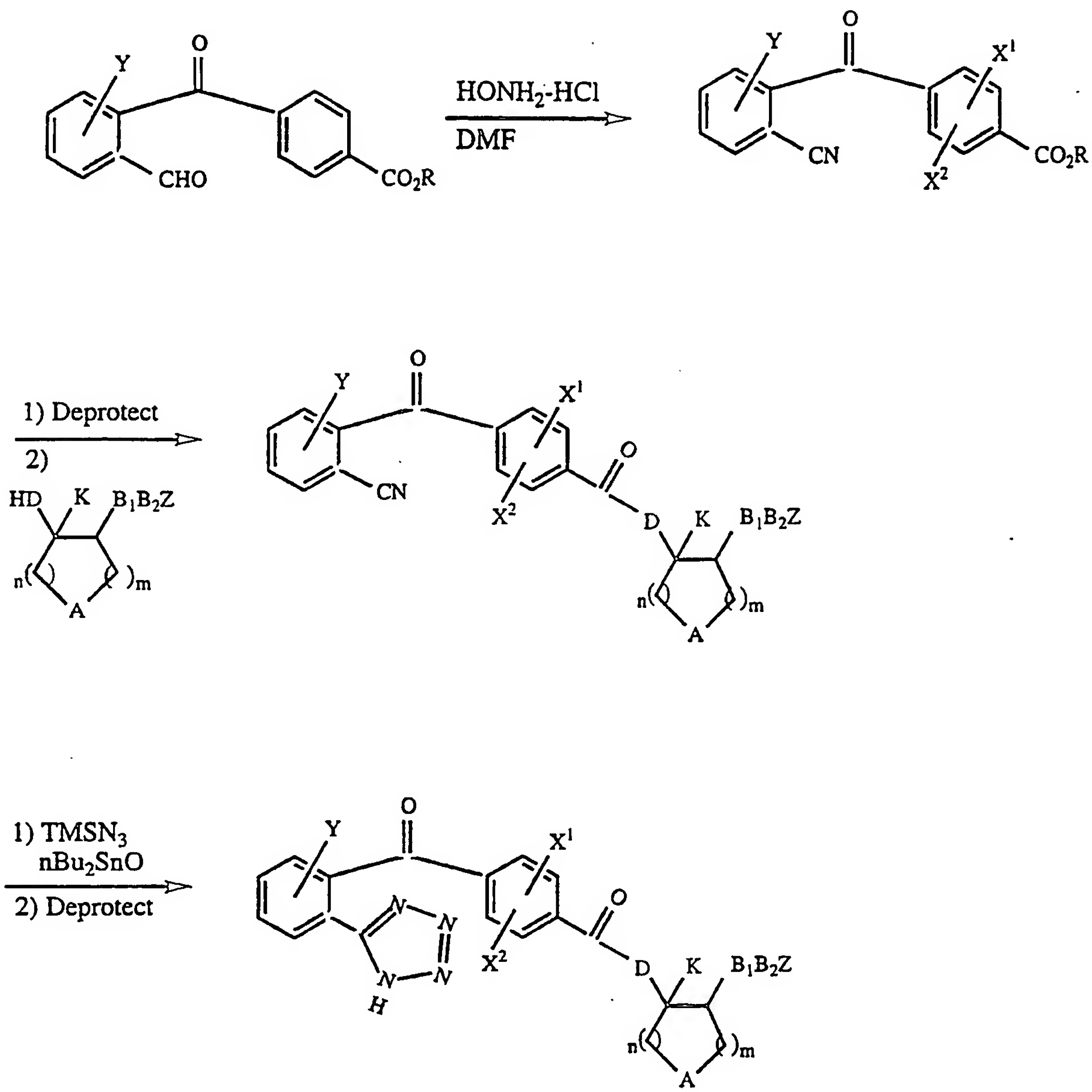




target where R = lower alkyl

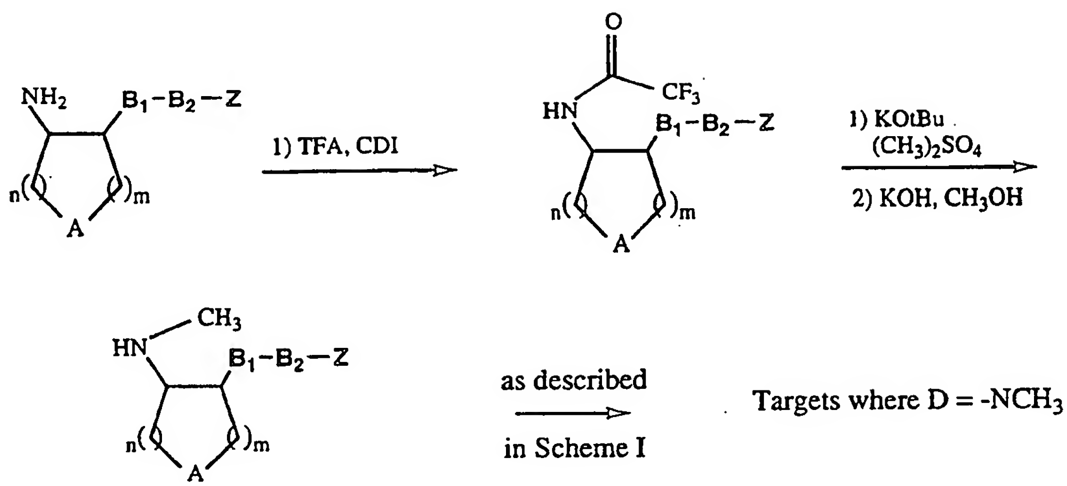
Scheme XXII describes the synthesis of compounds of the invention in which group G is substituted with a tetrazole ring. Keto aldehyde (prepared as described in Scheme IX F) is treated with hydroxylamine hydrochloride in dimethylformamide to provide the nitrile. Following deprotection to the acid, it is coupled to provide target compounds wherein G is substituted with a nitrile group. Treatment with trimethylsilylazide and nBu_2SnO followed by deprotection affords the target compounds.

Scheme XXII


Y
O
CHO
CO2R
HONH2-HCl
DMF
Y
O
X1
CN
X2
CO2R
1) Deprotect
2)
HD
K
B1B2Z
n(
)m
A
Y
O
X1
CN
X2
O
D
K
B1B2Z
n(
)m
A
1) TMSN3
nBu2SnO
2) Deprotect
Y
O
X1
N
N
N
N
H
X2
O
D
K
B1B2Z
n(
)m
A

Scheme XXIII provides a synthetic scheme for the preparation of compounds where D is N-R. Amine intermediate (prepared as described in Scheme III) is converted to the trifluoroacetamide. Treatment with a strong base, such as KOtBu and an alkylating agent such as methyl iodide or dimethylsulfate followed by cleavage of the trifluorocetamide provides the intermediate amine wherein D is N-R. This is converted to compounds of the invention using procedures outlined in Scheme III.

Scheme XXIII



Persons of ordinary skill in the art will recognize that the foregoing schemes are exemplary only and should not be construed to be limiting.

Pharmaceutical preparations incorporating compounds according to the present invention can be used to block PKC activity related to abnormal or undesirable cellular events and activity including tumorogeneis and cellular activity related to inflammation and reperfusion injury. Treatment of disorders and disease conditions can be performed by administration of effective amounts of pharmaceutical preparation that comprise compounds according to the present invention. Compounds can be formulated for human and animal prophylactic and therapeutic applications by those having ordinary skill in the art. The range of amounts of a compound to be administered to mammals, particularly humans, to be effective in inflammatory, tumor or reperfusion injury therapy can routinely be determined by those having ordinary skill in the art.

The compounds and pharmaceutical compositions of the invention may be administered by any method that produces contact of the active ingredient with the agent's site of action in the body of a mammal or in a body fluid or tissue. These methods include but not limited to oral, topical, hypodermal, intravenous, intramuscular and intraparenteral methods of administration. The compounds may be administered singly or in combination with other compounds of the invention, other pharmaceutical compounds such as chemotherapeutic compounds, or in conjunction with therapies such as radiation treatment. The compounds of the invention are preferably administered with a pharmaceutically acceptable carrier selected on the basis of the selected route of administration and standard pharmaceutical practice.

The compounds of the invention are administered to mammals, preferably humans, in therapeutically effective amounts which are effective to inhibit protein kinase C, to inhibit tumor cell growth, inhibit inflammation of tissue, inhibit keratinocyte cell proliferation, inhibit oxidative burst from neutrophils or inhibit platelet aggregation. The

dosage administered in any particular instance will depend upon factors such as the pharmacodynamic characteristics of the compound of the invention, its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms; kind of concurrent treatment, frequency of treatment, and the effect desired.

Compounds according to the present invention inhibit the activity of PKC in cells. The range of the amount of inhibitory compound that is effective for inhibiting PKC activity can be determined by one having ordinary skill in the art. By inhibiting PKC activity, balanoids are useful in the treatment of disease conditions in which control of cellular growth, regulation and/or differentiation is desirable. An effective amount of a balanoid can be administered to mammals who are suffering from inflammatory, cardiovascular or neoplastic diseases, particularly inflammation, reperfusion injury and cancer, in order to counter the disease at the cellular level.

It is contemplated that the daily dosage of a compound of the invention will be in the range of from about 1 μg to about 100 mg per kg of body weight, preferably from about 1 μg to about 40 mg per kg body weight, more preferably from about 10 μg to about 20 mg per kg per day.

Pharmaceutical compositions of the invention may be administered in a single dosage, divided dosages or in sustained release forms. Persons of ordinary skill will be able to determine dosage forms and amounts with only routine experimentation based upon the considerations of this invention. Isomers of the compounds and pharmaceutical compositions, particularly optically active stereoisomers, are also within the scope of the present invention.

The compounds of the invention may be administered as a pharmaceutical composition orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. The compounds may also be administered parenterally in sterile liquid dosage forms or topically in a carrier. The compounds of the

invention may be formulated into dosage forms according to standard practices in the field of pharmaceutical preparations. See *Remington's Pharmaceutical Sciences*, A. Osol, Mack Publishing Company, Easton, Pennsylvania.

Compounds of the invention may be mixed with powdered carriers, such as lactose, sucrose, mannitol, starch, cellulose derivatives, magnesium stearate, and stearic acid for insertion into gelatin capsules, or for forming into tablets. Both tablets and capsules may be manufactured as sustained release products for continuous release of medication over a period of hours. Compressed tablets can be sugar or film coated to mask any unpleasant taste and protect the tablet from the atmosphere or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration may contain coloring and flavoring to increase patient acceptance, in addition to a pharmaceutically acceptable diluent such as water, buffer or saline solution.

For parenteral administration, a compound of the invention may be mixed with a suitable carrier or diluent such as water, an oil, saline solution, aqueous dextrose (glucose) and related sugar solutions, glycols such as propylene glycol or polyethylene glycols. Solutions for parenteral administration contain preferably a water soluble salt of the compound of the invention. Stabilizing agents, antioxidizing agents and preservatives may also be added. Suitable antioxidizing agents include sodium bisulfite, sodium sulfite, and ascorbic acid, citric acid and its salts, and sodium EDTA. Suitable preservatives include benzalkonium chloride, methyl-or propyl-paraben, and chlorbutanol.

Animal studies have shown that perhaps 50% or more of ischemic-related myocardial damage can be attributed to polymorphonuclear leukocytes (neutrophils) which accumulate at the site of occlusion. Damage from the accumulated neutrophils may be due to the release of proteolytic enzymes from the activated neutrophils or the release of reactive oxygen intermediates (ROI). Much of the "no reflow" phenomenon

associated with myocardial ischemia is attributed to myocardial capillary plugging. The plugging of capillaries has been attributed to both aggregated platelets and aggregated neutrophils. Although both cell types are aggregate during the ischemic event, the relative contribution of each to capillary plugging has not yet been established. It is accepted that the damage by neutrophils to myocardial tissue proceeds through a cascade of events, one of the earliest being the bonding of activated neutrophils to damaged vascular endothelium. However the binding of the neutrophils is significantly enhanced by their activation. Thus, an even earlier event is the generation of molecules (such as cytokines, and chemotactic factors) which can function as activation stimuli. These molecules probably originate from damaged and aggregated platelets, from damaged vascular endothelium, or from the oxidation of plasma proteins or lipids by endothelial-derived oxidants.

Strategies for overcoming the deleterious effects of reactive oxygen intermediates have centered on the development of scavengers for the molecules. Superoxide dismutase (SOD) has been shown to be a particularly effective scavenger of superoxide, but suffers from a very short half-life in the blood. Several companies have approached this problem by creating versions of the enzyme with increased half-lives by techniques such as liposome encapsulation or polyethylene glycol conjugation. Reports on the effectiveness of these new versions are mixed. Catalase, a scavenger of hydrogen peroxide, and hydroxyl radical scavengers have also been tested and found to be effective to varying degrees. However, none of the strategies designed to scavenge reactive oxygen intermediates will prevent the aggregation of platelets, the release of chemotactic molecules, the activation and adherence of neutrophils to vascular endothelium, or the release of proteolytic enzymes from activated neutrophils.

One advantage of protein kinase C inhibitors as therapeutics for reperfusion injury is that they have been demonstrated to: 1) block platelet aggregation and release of

neutrophil activating agents such as PAF; 2) block neutrophil activation, chemotactic migration, and adherence to activated or damaged endothelium; and 3) block neutrophil release of proteolytic enzymes and reactive oxygen intermediates. Thus, these agents have the capability of blocking all three of the most significant mechanisms of pathogenesis associated with reperfusion injury and should thus have a decided therapeutic advantage.

The table below contains a list of compounds according to the present invention. For convenience, in some cases the substituient groups described in their noun form rather than as adjectives, e.g. pyridine rather than pyridyl. It is to be understood that, unless specified, points of attachment of these functional groups can be any which are typically found in organic chemistry. Thus, for example, recitation of "pyridine" as a substituient comprehends attachment at the 2, 3, or 4 position.

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
1	NH	NH	CO	p-hydroxy phenyl	O	2,6-dihydroxy phenyl	CO	2-hydroxy phenyl	CO	H	1	3
2	NH	NH	CO	p-hydroxy phenyl	O	2,6-dihydroxy phenyl	CO	2-hydroxy phenyl	CO	H	1	3
3	NH	NH	SO_2	p-methyl phenyl	O	2,6-dihydroxy phenyl	CO	2-hydroxy phenyl	CO	H	1	3
4	NH	NH	CO	p-hydroxy phenyl	O	2,6-dihydroxy phenyl	CO	phenyl	CO	H	1	3
5	CH_2	NH	CO	p-hydroxy phenyl	O	2,6-dihydroxy phenyl	CH_2	phenyl	CO	H	1	3
6	CH_2	NH	CO	p-hydroxy phenyl	O	2,6-dihydroxy phenyl	CO	2-hydroxy phenyl	CO	H	1	3
7	CH_2	NH	CO	p-hydroxy phenyl	O	2,6-dihydroxy phenyl	CO	2-carboxy phenyl	CO	H	1	3
8	NH	NH	CO	p-hydroxy phenyl	O	2,6-dihydroxy phenyl	CO	2-carboxy phenyl	CO	H	1	3
9	NH	NH	CO	pyridine	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy benzene	CO	H	1	3
10	NH	NH	CO	pyrrole	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
11	NH	NH	CO	oxazole	O	3,5-dimethoxy phenyl	CO	2-carboxy-6-methyl phenyl	CO	H	1	3
12	NH	NH	CO	indole	O	3-hydroxy-5-methylphenyl	CO	2-hydroxy-6-methyl phenyl	CO	H	1	3
13	NH	NH	CO	purine	O	3-methoxy-5-methylphenyl	CO	2,6-dimethyl phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
14	NH	NH	CO	furan	O	3-hydroxy phenyl	CO	2,6-dimethoxy phenyl	CO	H	1	3
15	NH	NH	CO	thiophene	O	3,5-dihydroxy phenyl	CO	2,6-dihydroxy phenyl	CO	H	1	3
16	NH	NH	CO	pyridazine	O	3,5-dimethoxy phenyl	CO	2-carboxy-6-hydroxy benzene	CO	H	1	3
17	NH	NH	CO	pyrimidine	O	3-hydroxy-5-methylphenyl	CO	2-carboxy-6-hydroxy benzene	CO	H	1	3
18	NH	NH	CO	pyrazine	O	3,5-dimethoxy phenyl	CO	2-carboxy-6-hydroxy benzene	CO	H	1	3
19	NH	NH	CO	imidazole	O	3-hydroxy-5-methylphenyl	CO	2-carboxy-6-hydroxy benzene	CO	H	1	3
20	NH	NH	CO	thiazole	O	3,5-dihyroxy benzene	CO	2-carboxy-6-hydroxy benzene	CO	H	1	3
21	NH	NH	CO	isoxazole	O	3,5-dimethoxy phenyl	CO	2-carboxy-6-hydroxy benzene	CO	H	1	3
22	NH	NH	CO	pyrazole	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy benzene	CO	H	1	3
23	NH	NH	CO	isothiazole	O	3,5-dihydroxy benzene	CO	2-carboxy-6-hydroxy benzene	CO	H	1	3
24	NH	NH	CO	benzene	O	3,5-dimethoxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
25	NH	NH	CO	methyl benzene	O	3-hydroxy-5-methylphenyl	CO	2,6-dimethyl phenyl	CO	H	1	3
26	NH	NH	CO	dimethyl benzene	O	3,5-dimethoxy phenyl	CO	2,6-dimethoxy phenyl	CO	H	1	3
27	NH	NH	CO	trimethyl benzene	O	3,5-dihydroxy benzene	CO	2-carboxy-6-hydroxy benzene	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
28	NH	NH	CO	tetramethyl	O	3-hydroxy-5-methylphenyl	CO	2-carboxy-6-hydroxy benzene	CO	H	1	3
29	NH	NH	CO	ethyl benzene	O	3,5-dihydroxy benzene	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
30	NH	NH	CO	tetraethyl benzene	O	3-hydroxy phenyl	CO	2-carboxy-6-hydroxy benzene	CO	H	1	3
31	NH	NH	CO	propyl benzene	O	3,5-dihydroxy phenyl	CO	2,6-dihydroxy phenyl	CO	H	1	3
32	NH	NH	CO	tetra propyl benzene	O	3,5-dihydroxy benzene	CO	2-carboxy-6-methyl phenyl	CO	H	1	3
33	NH	NH	CO	butyl benzene	O	3-hydroxy-5-methoxy phenyl	CO	2-carboxy-6-hydroxy benzene	CO	H	1	3
34	NH	NH	CO	tetrabutyl benzene	O	3,5-dihydroxy benzene	CO	2-carboxy-6-hydroxy benzene	CO	H	1	3
35	NH	NH	CO	pentyl benzene	O	3,5-dihydroxy benzene	CO	2-carboxy-6-hydroxy benzene	CO	H	1	3
36	NH	NH	CO	tetrapentyl benzene	O	3,5-dihydroxy phenyl	CO	2,6-dimethoxy phenyl	CO	H	1	3
37	NH	NH	CO	methoxy benzene	O	3,5-dihydroxy benzene	CO	2,6-dimethyl phenyl	CO	H	1	3
38	NH	NH	CO	dimethoxy benzene	O	3,5-dimethoxy phenyl	CO	2-carboxy-6-methyl phenyl	CO	H	1	3
39	NH	NH	CO	trimethoxy benzene	O	3,5-dihydroxy benzene	CO	2-carboxy-6-methoxy phenyl	CO	H	1	3
40	NH	NH	CO	tetra methyl benzene	O	3-hydroxy-5-methoxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
41	NH	NH	CO	ethoxy benzene	O	3,5-dihydroxy benzene	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
42	NH	NH	CO	diethoxy benzene	O	3-hydroxy-5-methyl phenyl	CO	2-carboxy-6-methoxy phenyl	CO	H	1	3
43	NH	NH	CO	nitro benzene	O	3,5-dihydroxy benzene	CO	2,6-dimethyl phenyl	CO	H	1	3
44	NH	NH	CO	dinitro benzene	O	3-methoxy-5-methyl phenyl	CO	2-carboxy-6-hydroxy benzene	CO	H	1	3
45	NH	NH	CO	halo benzene	O	3,5-dihydroxy benzene	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
46	NH	NH	CO	dihalo benzene	O	3-hydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
47	NH	NH	CO	trihalo benzene	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
48	NH	NH	CO	tetrahalo benzene	O	3,5-dihydroxy benzene	CO	2-carboxy-6-methoxy phenyl	CO	H	1	3
49	NH	NH	CO	benzene carboxylic acid	O	3,5-dimethoxy phenyl	CO	2-carboxy-6-methoxy phenyl	CO	H	1	3
50	NH	NH	CO	benzene dicarboxylic acid	O	3,5-dihydroxy benzene	CO	2-carboxy-6-methyl phenyl	CO	H	1	3
51	NH	NH	CO	benzamide amido benzene	O	3-methoxy-5-methyl phenyl	CO	2-hydroxy-6-methyl phenyl	CO	H	1	3
52	NH	NH	CO	benzene diamide	O	3-hydroxy phenyl	CO	2,6-dimethyl phenyl	CO	H	1	3
53	NH	NH	CO	phenol	O	3,5-dihydroxy benzene	CO	2,6-dimethoxy phenyl	CO	H	1	3
54	NH	NH	CO	dihydroxy benzene	O	3,5-dihydroxy phenyl	CO	2,6-dihydroxy phenyl	CO	H	1	3
55	NH	NH	CO	trihydroxy benzene	O	3,5-dihydroxy benzene	CO	2-carboxy-6-methoxy phenyl	CO	H	1	3

Cmpd. ∅	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
56	NH	NH	CO	pentahydroxy benzene	O	3-hydroxy-5-methyl phenyl	CO	2-carboxy-6-methoxy phenyl	CO	H	1	3
57	NH	NH	CO	triethoxy benzene	O	3,5-dihydroxy benzene	CO	2,6-dimethyl phenyl	CO	H	1	3
58	NH	NH	CO	tetra ethoxy benzene	O	3-hydroxy phenyl	CO	2,6-dihydroxy phenyl	CO	H	1	3
59	NH	NH	CO	propoxy benzene	O	3,5-dihydroxy benzene	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
60	NH	NH	CO	dipropoxy benzene	O	3-methoxy-5-methyl phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
61	NH	NH	CO	tripropoxy benzene	O	3,5-dihydroxy benzene	CO	2-carboxy-6-methyl phenyl	CO	H	1	3
62	NH	NH	CO	tetra propoxy benzene	O	3,5-dihydroxy phenyl	CO	2,6-dimethoxy phenyl	CO	H	1	3
63	NH	NH	CO	amidine	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
64	NH	NH	CO	diamino benzene	O	3,5-dihydroxy benzene	CO	2-hydroxy-6-methyl phenyl	CO	H	1	3
65	NH	NH	CO	methoxy pyridine	O	3,5-dihydroxy benzene	CO	2-carboxy-6-methyl phenyl	CO	H	1	3
66	NH	NH	CO	dimethoxy pyridine	O	3-hydroxy-5-methoxy phenyl	CO	2-carboxy-6-methoxy phenyl	CO	H	1	3
67	NH	NH	CO	hydroxy pyridine	O	3,5-dihydroxy benzene	CO	2,6-dihydroxy phenyl	CO	H	1	3
68	NH	NH	CO	dihydroxy pyridine	O	3,5-dihydroxy benzene	CO	2,6-dimethoxy phenyl	CO	H	1	3
69	NH	NH	CO	ethoxy pyrrole	O	3,5-dihydroxy phenyl	CO	2-hydroxy-6-methyl phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
70	NH	NH	CO	dihydroxy pyrrole	O	3,5-dihydroxy benzene	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
71	NH	NH	CO	dimethoxy indole	O	3-hydroxy-5-methoxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
72	NH	NH	CO	hydroxy purine	O	3,5-dihydroxy benzene	CO	2-carboxy-6-methyl phenyl	CO	H	1	3
73	NH	NH	CO	dimethoxy furan	O	3-methoxy-5-methyl phenyl	CO	2-carboxy-6-methoxy phenyl	CO	H	1	3
74	NH	NH	CO	hydroxy thiophene	O	3,5-dihydroxy benzene	CO	2,6-dimethyl phenyl	CO	H	1	3
75	NH	NH	CO	methoxy pyridazine	O	3,5-dihydroxy benzene	CO	2,6-dihydroxy phenyl	CO	H	1	3
76	NH	NH	CO	dimethoxy pyridazine	O	3-hydroxy phenyl	CO	2,6-dimethoxy phenyl	CO	H	1	3
77	NH	NH	CO	hydroxy pyrimidine	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
78	NH	NH	CO	diamido pyrimidine	O	3,5-dihydroxy benzene	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
79	NH	NH	CO	amido pyrazine	O	3,5-dimethoxy phenyl	CO	2-carboxy-6-methoxy phenyl	CO	H	1	3
80	NH	NH	CO	diethoxy pyrazine	O	3,5-dihydroxy benzene	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
81	NH	NH	CO	p-hydroxy phenyl	O	pyridine	CO	2-carboxy-6-methyl phenyl	CO	H	1	3
82	NH	NH	CO	p-methoxy phenyl	O	pyrrole	CO	2-hydroxy-6-methyl phenyl	CO	H	1	3
83	NH	NH	CO	p-chloro phenyl	O	oxazole	CO	2,6-dimethoxy phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
84	NH	NH	CO	m-methoxy phenyl	O	indole	CO	2,6-dihydroxy phenyl	CO	H	1	3
85	NH	NH	CO	m-hydroxy phenyl	O	purine	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
86	NH	NH	CO	m-chloro phenyl	O	furan	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
87	NH	NH	CO	o-methoxy phenyl	O	thiophene	CO	2-hydroxy-6-methyl phenyl	CO	H	1	3
88	NH	NH	CO	o-hydroxy phenyl	O	pyridazine	CO	2,6-dimethyl phenyl	CO	H	1	3
89	NH	NH	CO	o-chloro phenyl	O	pyrimidine	CO	2,6-dimethoxy phenyl	CO	H	1	3
90	NH	NH	CO	p-hydroxy phenyl	O	pyrazine	CO	2-carboxy-6-methoxy phenyl	CO	H	1	3
91	NH	NH	CO	m-methoxy phenyl	O	imidazole	CO	2,6-dimethyl phenyl	CO	H	1	3
92	NH	NH	CO	m-hydroxy phenyl	O	thiazole	CO	2-carboxy-6-methyl phenyl	CO	H	1	3
93	NH	NH	CO	p-methoxy phenyl	O	isoxazole	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
94	NH	NH	CO	o-methoxy phenyl	O	pyrazole	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
95	NH	NH	CO	m-hydroxy phenyl	O	isothiazole	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
96	NH	NH	CO	o-methoxy phenyl	O	benzene	CO	2-carboxy-6-methyl benzene	CO	H	1	3
97	NH	NH	CO	o-chloro phenyl	O	methyl benzene	CO	2-carboxy-6-methyl benzene	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
98	NH	NH	CO	p-hydroxy phenyl	O	dimethyl benzene	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
99	NH	NH	CO	p-chloro phenyl	O	trimethyl benzene	CO	2-carboxy-6-methyl phenyl	CO	H	1	3
100	NH	NH	CO	m-hydroxy phenyl	O	tetramethyl	CO	2-hydroxy-6-methyl phenyl	CO	H	1	3
101	NH	NH	CO	m-methoxy phenyl	O	ethyl benzene	CO	2,6-dimethoxy phenyl	CO	H	1	3
102	NH	NH	CO	p-hydroxy phenyl	O	tetraethyl benzene	CO	2-carboxy-6-methoxy phenyl	CO	H	1	3
103	NH	NH	CO	p-methoxy phenyl	O	propyl benzene benzene	CO	2,6-dihydroxy phenyl	CO	H	1	3
104	NH	NH	CO	m-hydroxy phenyl	O	tetra propyl benzene	CO	2-hydroxy-6-methyl phenyl	CO	H	1	3
105	NH	NH	CO	o-hydroxy phenyl	O	butyl benzene	CO	2,6-dihydroxy phenyl	CO	H	1	3
106	NH	NH	CO	m-hydroxy phenyl	O	tetrabutyl benzene	CO	2-carboxy-6-methyl benzene	CO	H	1	3
107	NH	NH	CO	m-hydroxy phenyl	O	pentyl benzene	CO	2-carboxy-6-methyl benzene	CO	H	1	3
108	NH	NH	CO	o-hydroxy phenyl	O	tetrapentyl benzene	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
109	NH	NH	CO	o-chloro phenyl	O	methoxy benzene	CO	2-carboxy-6-methoxy phenyl	CO	H	1	3
110	NH	NH	CO	p-methoxy phenyl	O	dimethoxy benzene	CO	2-hydroxy-6-methyl phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
111	NH	NH	CO	p-chloro phenyl	O	trimethoxy benzene	CO	2,6-dimethyl phenyl	CO	H	1	3
112	NH	NH	CO	p-hydroxy phenyl	O	tetra methyl benzene	CO	2,6-dihydroxy phenyl	CO	H	1	3
113	NH	NH	CO	p-methoxy phenyl	O	ethoxy benzene	CO	2-carboxy-6-methyl benzene	CO	H	1	3
114	NH	NH	CO	p-hydroxy phenyl	O	diethoxy benzene	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
115	NH	NH	CO	m-hydroxy phenyl	O	nitro benzene	CO	2-carboxy-6-methoxy phenyl	CO	H	1	3
116	NH	NH	CO	p-chloro phenyl	O	dinitro benzene	CO	2,6-dimethyl phenyl	CO	H	1	3
117	NH	NH	CO	o-methoxy phenyl	O	halo benzene	CO	2-hydroxy-6-methyl phenyl	CO	H	1	3
118	NH	NH	CO	p-methoxy phenyl	O	dihalo benzene	CO	2-carboxy-6-methyl phenyl	CO	H	1	3
119	NH	NH	CO	p-hydroxy phenyl	O	trihalo benzene	CO	2-hydroxy-6-methyl phenyl	CO	H	1	3
120	NH	NH	CO	o-chloro phenyl	O	tetrahalo benzene	CO	2-carboxy-6-methoxy phenyl	CO	H	1	3
121	NH	NH	CO	m-hydroxy phenyl	O	carboxy acid benzene	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
122	NH	NH	CO	m-chloro phenyl	O	dicarboxyacid benzene	CO	2-carboxy-6-ethyl benzene	CO	H	1	3
123	NH	NH	CO	p-hydroxy phenyl	O	amido benzene	CO	2,6-dimethoxy phenyl	CO	H	1	3
124	NH	NH	CO	o-methoxy phenyl	O	diamido benzene	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
125	NH	NH	CO	p-hydroxy phenyl	O	phenol	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
126	NH	NH	CO	m-methoxy phenyl	O	dihydroxy benzene	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
127	NH	NH	CO	p-methoxy phenyl	O	trihydroxy benzene	CO	2-carboxy-6-propoxy benzene	CO	H	1	3
128	NH	NH	CO	m-methoxy phenyl	O	tetrahydroxy benzene	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
129	NH	NH	CO	p-chloro phenyl	O	triethoxy benzene	CO	2,6-dimethyl phenyl	CO	H	1	3
130	NH	NH	CO	p-methoxy phenyl	O	tetra ethoxy benzene	CO	2-carboxy-6-methoxy phenyl	CO	H	1	3
131	NH	NH	CO	p-hydroxy phenyl	O	pentoxy benzene	CO	2,6-dihydroxy phenyl	CO	H	1	3
132	NH	NH	CO	p-hydroxy phenyl	O	dipentoxy benzene	CO	2,6-dimethoxy phenyl	CO	H	1	3
133	NH	NH	CO	m-methoxy phenyl	O	tripentoxy benzene	CO	2-carboxy-6-ethyl benzene	CO	H	1	3
134	NH	NH	CO	o-hydroxy phenyl	O	tetrapentoxy benzene	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
135	NH	NH	CO	o-hydroxy phenyl	O	aniline	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
136	NH	NH	CO	o-chloro phenyl	O	diamino benzene	CO	2,6-dimethoxy phenyl	CO	H	1	3
137	NH	NH	CO	p-methoxy phenyl	O	methoxy pyridine	CO	2-carboxy-6-propyl benzene	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
138	NH	NH	CO	p-hydroxy phenyl	O	dimethoxy pyridine	CO	2-carboxy-6-methyl phenyl	CO	H	1	3
139	NH	NH	CO	p-chloro phenyl	O	hydroxy pyridine	CO	2-carboxy-6-methoxy phenyl	CO	H	1	3
140	NH	NH	CO	p-chloro phenyl	O	dihydroxy pyridine	CO	2-carboxy-6-methyl phenyl	CO	H	1	3
141	NH	NH	CO	m-hydroxy phenyl	O	ethoxy pyrrole	CO	2-hydroxy-6-methyl phenyl	CO	H	1	3
142	NH	NH	CO	m-methoxy phenyl	O	dihydroxy pyrrole	CO	2,6-dihydroxy phenyl	CO	H	1	3
143	NH	NH	CO	o-hydroxy phenyl	O	dimethoxy indole	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
144	NH	NH	CO	o-chloro phenyl	O	hydroxy purine	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
145	NH	NH	CO	m-chloro phenyl	O	demethoxy furan	CO	2-hydroxy-6-methyl phenyl	CO	H	1	3
146	NH	NH	CO	o-methoxy phenyl	O	hydroxy thiophene	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
147	NH	NH	CO	p-hydroxy phenyl	O	2,6-dihydroxy phenyl-4-	CO	2-hydroxyphenyl-6-carboxylic acid	CO	H	1	3
148	NH	NH	CO	p-chloro phenyl	O	methoxy pyridazine	CO	2-carboxy benzene	CO	H	1	3
149	NH	NH	CO	m-hydroxy phenyl	O	hydroxy pyrimidine	CO	2-carboxy-6-methyl phenyl	CO	H	1	3
150	NH	NH	CO	p-methoxy phenyl	O	diamido pyrimidine	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
153	NH	NH	CO	o-methoxy phenyl	O	amido pyrazine	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
154	NH	NH	CO	m-chloro phenyl	O	diethoxy pyrazine	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
155	NH	NH	CO	o-methoxy phenyl	O	3,5-dihydroxy benzene	CO	pyridine	CO	H	1	3
156	NH	NH	CO	p-methoxy phenyl	O	3,5-dihydroxy benzene	CO	pyrrole	CO	H	1	3
157	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	oxazole	CO	H	1	3
158	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	indole	CO	H	1	3
159	NH	NH	CO	o-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	purine	CO	H	1	3
160	NH	NH	CO	m-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	furan	CO	H	1	3
161	NH	NH	CO	m-methoxy phenyl	O	3,5-dihydroxy benzene	CO	thiophene	CO	H	1	3
162	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	pyridazine	CO	H	1	3
163	NH	NH	CO	m-methoxy phenyl	O	3,5-dihydroxy benzene	CO	pyrimidine	CO	H	1	3
164	NH	NH	CO	p-methoxy phenyl	O	3,5-dihydroxy benzene	CO	pyrazine	CO	H	1	3
165	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	imidazole	CO	H	1	3

Cmpd. ∅	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
166	NH	NH	CO	p-chloro phenyl	O	3,5-dihydroxy benzene	CO	thiazole	CO	H	1	3
167	NH	NH	CO	m-methoxy phenyl	O	3,5-dihydroxy benzene	CO	isoxazole	CO	H	1	3
168	NH	NH	CO	p-chloro phenyl	O	3,5-dihydroxy benzene	CO	pyrazole	CO	H	1	3
169	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	isothiazole	CO	H	1	3
170	NH	NH	CO	p-methoxy phenyl	O	3,5-dihydroxy benzene	CO	benzene	CO	H	1	3
171	NH	NH	CO	o-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	methyl benzene	CO	H	1	3
172	NH	NH	CO	o-chloro phenyl	O	3,5-dihydroxy benzene	CO	dimethyl benzene	CO	H	1	3
173	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	trimethyl benzene	CO	H	1	3
174	NH	NH	CO	p-methoxy phenyl	O	3,5-dihydroxy benzene	CO	tetramethyl	CO	H	1	3
175	NH	NH	CO	m-methoxy phenyl	O	3,5-dihydroxy benzene	CO	ethyl benzene	CO	H	1	3
176	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	tetraethyl benzene	CO	H	1	3
177	NH	NH	CO	m-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	propyl benzene benzene	CO	H	1	3
178	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	tetra propyl benzene	CO	H	1	3
179	NH	NH	CO	p-chloro phenyl	O	3,5-dihydroxy benzene	CO	butyl benzene	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
180	NH	NH	CO	o-chloro phenyl	O	3,5-dihydroxy benzene	CO	tetrabutyl benzene	CO	H	1	3
181	NH	NH	CO	p-hydroxy phenyl	O	3,-53,5-dihydroxy benzene	CO	pentyl benzene	CO	H	1	3
182	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	tetrapentyl benzene	CO	H	1	3
183	NH	NH	CO	m-methoxy phenyl	O	3,5-dihydroxy benzene	CO	methoxy benzene	CO	H	1	3
184	NH	NH	CO	m-chloro phenyl	O	3,5-dihydroxy benzene	CO	dimethoxy benzene	CO	H	1	3
185	NH	NH	CO	o-methoxy phenyl	O	3,5-dihydroxy benzene	CO	trimethoxy benzene	CO	H	1	3
186	NH	NH	CO	o-chloro phenyl	O	3,5-dihydroxy benzene	CO	tetramethyl benzene	CO	H	1	3
187	NH	NH	CO	m-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	ethoxy benzene	CO	H	1	3
188	NH	NH	CO	p-chloro phenyl	O	3,5-dihydroxy benzene	CO	diethoxy benzene	CO	H	1	3
189	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	nitro benzene	CO	H	1	3
190	NH	NH	CO	p-methoxy phenyl	O	3,5-dihydroxy benzene	CO	dinitro benzene	CO	H	1	3
191	NH	NH	CO	o-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	halo benzene	CO	H	1	3
192	NH	NH	CO	o-chloro phenyl	O	3,5-dihydroxy benzene	CO	dihalo benzene	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
193	NH	NH	CO	m-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	trihalo benzene	CO	H	1	3
194	NH	NH	CO	m-chloro phenyl	O	3,5-dihydroxy benzene	CO	tetrahalo benzene	CO	H	1	3
195	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	carboxy acid benzene	CO	H	1	3
196	NH	NH	CO	p-chloro phenyl	O	3,5-dihydroxy benzene	CO	dicarboxyacid benzene	CO	H	1	3
197	NH	NH	CO	p-methoxy phenyl	O	3,5-dihydroxy benzene	CO	amido benzene	CO	H	1	3
198	NH	NH	CO	m-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	diamido benzene	CO	H	1	3
199	NH	NH	CO	m-chloro phenyl	O	3,5-dihydroxy benzene	CO	3,5-dihydroxy benzene	CO	H	1	3
200	NH	NH	CO	o-methoxy phenyl	O	3,5-dihydroxy benzene	CO	trihydroxy benzene	CO	H	1	3
2O2	NH	NH	CO	o-methoxy phenyl	O	3,5-dihydroxy benzene	CO	tetrahydroxy benzene	CO	H	1	3
202	NH	NH	CO	p-chloro phenyl	O	3,5-dihydroxy benzene	CO	pentahydroxy benzene	CO	H	1	3
203	NH	NH	CO	p-chloro phenyl	O	3,5-dihydroxy benzene	CO	triethoxy benzene	CO	H	1	3
204	NH	NH	CO	o-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	tetra ethoxy benzene	CO	H	1	3
205	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	pentoxy benzene	CO	H	1	3
206	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	dipentoxy benzene	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
207	NH	NH	CO	p-methoxy phenyl	O	3,5-dihydroxy benzene	CO	tripentoxy benzene	CO	H	1	3
208	NH	NH	CO	m-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	tetrapentoxy benzene	CO	H	1	3
209	NH	NH	CO	o-methoxy phenyl	O	3,5-dihydroxy benzene	CO	amino benzene	CO	H	1	3
210	NH	NH	CO	o-chloro phenyl	O	3,5-dihydroxy benzene	CO	diamino benzene	CO	H	1	3
211	NH	NH	CO	p-methoxy phenyl	O	3,5-dihydroxy benzene	CO	methoxy pyridine	CO	H	1	3
212	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	dimethoxy pyridine	CO	H	1	3
213	NH	NH	CO	p-methoxy phenyl	O	3,5-dihydroxy benzene	CO	hydroxy pyridine	CO	H	1	3
214	NH	NH	CO	p-methoxy phenyl	O	3,5-dihydroxy benzene	CO	dihydroxy pyridine	CO	H	1	3
215	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	ethoxy pyrrole	CO	H	1	3
216	NH	NH	CO	m-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	dihydroxy pyrrole	CO	H	1	3
217	NH	NH	CO	p-chloro phenyl	O	3,5-dihydroxy benzene	CO	dimethoxy indole	CO	H	1	3
218	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	hydroxy purine	CO	H	1	3
219	NH	NH	CO	p-methoxy phenyl	O	3,5-dihydroxy benzene	CO	demethoxy furan	CO	H	1	3
220	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	hydroxy thiophene	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
221	NH	NH	CO	m-chloro phenyl	O	3,5-dihydroxy benzene	CO	methoxy pyridazine	CO	H	1	3
222	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	dimethoxy pyridazine	CO	H	1	3
223	NH	NH	CO	p-chloro phenyl	O	3,5-dihydroxy benzene	CO	hydroxy pyrimidine	CO	H	1	3
224	NH	NH	CO	m-chloro phenyl	O	3,5-dihydroxy benzene	CO	diamido pyrimidine	CO	H	1	3
225	NH	NH	CO	o-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	amido pyrazine	CO	H	1	3
226	NH	NH	CO	m-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	diethoxy pyrazine	CO	H	1	3
227	NH	NH	CO	quinoline	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
228	NH	NH	CO	methoxy quinoline	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
229	NH	NH	CO	dimethoxy quinoline	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
230	NH	NH	CO	trimethoxy quinoline	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
231	NH	NH	CO	hydroxy quinoline	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
232	NH	NH	CO	dihydroxy quinoline	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
233	NH	NH	CO	ethoxy quinoline	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
234	NH	NH	CO	amino quinoline	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
235	NH	NH	CO	diamido quinoline	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
236	NH	NH	CO	trihalo quinoline	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
237	NH	NH	CO	quinoline carboxylic acid	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
238	NH	NH	CO	quinazoline	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
239	NH	NH	CO	methoxy quinazoline	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
240	NH	NH	CO	dimethoxy quinazoline	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
241	NH	NH	CO	trimethoxy quinazoline	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
242	NH	NH	CO	hydroxy quinazoline	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
243	NH	NH	CO	trihydroxy quinazoline	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
244	NH	NH	CO	tetraethoxy quinazoline	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
245	NH	NH	CO	diamino quinazoline	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
246	NH	NH	CO	triamido quinazoline	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
247	NH	NH	CO	tetrahalo quinazoline	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
248	NH	NH	CO	quinazoline dicarboxylic acid	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
249	NH	NH	CO	m-methoxy phenyl	O	quinoline	CO	phenyl	CO	H	1	3
250	NH	NH	CO	p-hydroxy phenyl	O	methoxy quinoline	CO	phenyl	CO	H	1	3
251	NH	NH	CO	p-hydroxy phenyl	O	dimethoxy quinoline	CO	phenyl	CO	H	1	3
252	NH	NH	CO	p-methoxy phenyl	O	trimethoxy quinoline	CO	phenyl	CO	H	1	3
253	NH	NH	CO	m-hydroxy phenyl	O	hydroxy quinoline	CO	phenyl	CO	H	1	3
254	NH	NH	CO	o-hydroxy phenyl	O	dihydroxy quinoline	CO	phenyl	CO	H	1	3
255	NH	NH	CO	o-chloro phenyl	O	ethoxy quinoline	CO	phenyl	CO	H	1	3
256	NH	NH	CO	m-hydroxy phenyl	O	amino quinoline	CO	phenyl	CO	H	1	3
257	NH	NH	CO	m-methoxy phenyl	O	diamido quinoline	CO	phenyl	CO	H	1	3
258	NH	NH	CO	p-methoxy phenyl	O	trihalo quinoline	CO	phenyl	CO	H	1	3
259	NH	NH	CO	m-methoxy phenyl	O	quinoline carboxylic acid	CO	phenyl	CO	H	1	3
260	NH	NH	CO	p-hydroxy phenyl	O	quinazoline	CO	phenyl	CO	H	1	3
261	NH	NH	CO	p-methoxy phenyl	O	methoxy quinazoline	CO	phenyl	CO	H	1	3
262	NH	NH	CO	p-methoxy phenyl	O	dimethoxy quinazoline	CO	phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
263	NH	NH	CO	m-chloro phenyl	O	trimethoxy quinazoline	CO	phenyl	CO	H	1	3
264	NH	NH	CO	m-methoxy phenyl	O	hydroxy quinazoline	CO	phenyl	CO	H	1	3
265	NH	NH	CO	p-chloro phenyl	O	trihydroxy quinazoline	CO	phenyl	CO	H	1	3
266	NH	NH	CO	o-methoxy phenyl	O	tetraethoxy quinazoline	CO	phenyl	CO	H	1	3
267	NH	NH	CO	m-chloro phenyl	O	diamino quinazoline	CO	phenyl	CO	H	1	3
268	NH	NH	CO	o-chloro phenyl	O	triamido quinazoline	CO	phenyl	CO	H	1	3
269	NH	NH	CO	m-chloro phenyl	O	tetrahalo quinazoline	CO	phenyl	CO	H	1	3
270	NH	NH	CO	p-hydroxy phenyl	O	quinazoline dicarboxylic acid	CO	phenyl	CO	H	1	3
271	NH	NH	CO	p-methoxy phenyl	O	3,5-dihydroxy benzene	CO	quinoline	CO	H	1	3
272	NH	NH	CO	p-chloro phenyl	O	3,5-dihydroxy benzene	CO	methoxy quinoline	CO	H	1	3
273	NH	NH	CO	o-methoxy phenyl	O	3,5-dihydroxy benzene	CO	dimethoxy quinoline	CO	H	1	3
274	NH	NH	CO	o-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	trimethoxy quinoline	CO	H	1	3
275	NH	NH	CO	o-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	hydroxy quinoline	CO	H	1	3

Cmpd. #	A	B1	B2	Z	D	E	F	G	X	K	m	n
276	NH	NH	CO	m-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	dihydroxy quinoline	CO	H	1	3
277	NH	NH	CO	p-methoxy phenyl	O	3,5-dihydroxy benzene	CO	ethoxy quinoline	CO	H	1	3
278	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	amino quinoline	CO	H	1	3
279	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	diamido quinoline	CO	H	1	3
280	NH	NH	CO	p-chloro phenyl	O	3,5-dihydroxy benzene	CO	trihalo quinoline	CO	H	1	3
281	NH	NH	CO	m-methoxy phenyl	O	3,5-dihydroxy benzene	CO	quinoline carboxylic acid	CO	H	1	3
282	NH	NH	CO	m-chloro phenyl	O	3,5-dihydroxy benzene	CO	quinazoline	CO	H	1	3
283	NH	NH	CO	p-chloro phenyl	O	3,5-dihydroxy benzene	CO	methoxy quinazoline	CO	H	1	3
284	NH	NH	CO	o-methoxy phenyl	O	3,5-dihydroxy benzene	CO	dimethoxy quinazoline	CO	H	1	3
285	NH	NH	CO	m-chloro phenyl	O	3,5-dihydroxy benzene	CO	trimethoxy quinazoline	CO	H	1	3
286	NH	NH	CO	o-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	hydroxy quinazoline	CO	H	1	3
287	NH	NH	CO	o-chloro phenyl	O	3,5-dihydroxy benzene	CO	trihydroxy quinazoline	CO	H	1	3
288	NH	NH	CO	m-methoxy phenyl	O	3,5-dihydroxy benzene	CO	tetraethoxy quinazoline	CO	H	1	3
289	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	diamino quinazoline	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
290	NH	NH	CO	p-methoxy phenyl	O	3,5-dihydroxy benzene	CO	triamido quinazoline	CO	H	1	3
291	NH	NH	CO	p-chloro phenyl	O	3,5-dihydroxy benzene	CO	tetrahalo quinazoline	CO	H	1	3
292	NH	NH	CO	m-methoxy phenyl	O	3,5-dihydroxy benzene	CO	quinazoline dicarboxylic acid	CO	H	1	3
293	CH_2	O	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	O	phenyl	CO	H	1	3
294	CH_2	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
295	O	NH	CO	p-chloro phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
296	S	NH	CO	o-methoxy phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
297	N-phenyl sulfonyl	NH	CO	m-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
298	N-acetyl	NH	CO	m-methoxy phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
299	N-ureido	NH	CO	p-methoxy phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
300	N-phenyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
301	N-benzyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
302	NH	CH_2	CO	p-chloro phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3

Cmpd. ♯	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
303	NH	O	CO	m-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
304	NH	N-ethyl	CO	o-chloro phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
305	NH	N-methyl	CO	m-methoxy phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
306	N-anisyl	N-phenyl	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	quinazoline dicarboxylic acid	CO	H	1	3
307	NH	NH	CS	p-chloro phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
308	NH	NH	CO	p-hydroxy phenyl	CH_2	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
309	NH	NH	CO	p-hydroxy phenyl	N-ethyl	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
310	NH	NH	CO	p-methoxy phenyl	N-phenyl	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
311	NH	NH	CO	o-methoxy phenyl	N-propyl	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	3
312	NH	NH	CO	m-chloro phenyl	O	3,5-dihydroxy benzene	CS	phenyl	CO	H	1	3
313	NH	NH	CO	m-chloro phenyl	O	3,5-dihydroxy benzene	$CH(OCH_3)$	phenyl	CO	H	1	3
314	NH	NH	CO	o-chloro phenyl	O	3,5-dihydroxy benzene	CH(O-phenyl)	phenyl	CO	H	1	3
315	NH	NH	CO	o-hydroxy phenyl	O	3,5-dihydroxy benzene	CH_2	phenyl	CO	H	1	3
316	NH	NH	CO	m-chloro phenyl	O	3,5-dihydroxy benzene	O	phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
317	NH	NH	CO	m-hydroxy phenyl	O	3,5-dihydroxy benzene	S	phenyl	CO	H	1	3
318	NH	NH	CO	p-chloro phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	1
319	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	2
320	NH	NH	CO	p-methoxy phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	1	4
321	NH	NH	CO	o-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	2	1
322	NH	NH	CO	o-methoxy phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	3	1
323	NH	NH	CO	m-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	4	1
324	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	2	2
325	NH	NH	CO	p-methoxy phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	3	2
326	NH	NH	CO	m-chloro phenyl	O	3,5-dihydroxy benzene	CO	phenyl	CO	H	2	3
327	S	NH	CO	furan	O	thiazole	CO	phenyl	CO	H	1	3
328	$N-SO_2$ phenyl	NH	CS	thiophene	O	isoxazole	CS	phenyl	CO	H	1	1
329	N-acetyl	NH	CO	pyridazine	O	pyrazole	CO	phenyl	CS	H	1	1
330	N-ureido	NH	CS	pyrimidine	O	isothiazole	S	methoxy pyridine	CO	H	1	2
331	N-phenyl	CH_2	CO	pyrazine	O	benzene	CO	dimethoxy pyridine	CS	H	1	1

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
332	N-pyridyl	O	CS	imidazole	O	methyl benzene	CS	hydroxy pyridine	CO	H	1	2
333	O	O	CO	thiazole	O	dimethyl benzene	O	dihydroxy pyridine	CS	H	1	2
334	CH_2	N-phenyl	CS	isoxazole	O	trimethyl benzene	NH	ethoxy pyrrole	CO	H	1	1
335	NH	N-ethyl	CO	pyrazole	O	tetramethyl	CO	dihydroxy pyrrole	CS	H	1	2
336	NH	NH	CS	isothiazole	O	ethyl benzene	CS	dimethoxy indole	CO	H	1	1
337	NH	N-phenyl	CO	benzene	O	tetraethyl benzene	CO	hydroxy purine	CS	H	1	3
338	NH	N-pyridyl	CS	methyl benzene	O	propyl benzene benzene	N-methoxy methyl	dimethoxy furan	CO	H	1	3
339	CH_2	NH	CO	dimethyl benzene	O	tetra propyl benzene	CO	hydroxy thiophene	CS	H	1	3
340	O	NH	CS	phenyl	O	butyl benzene	N-pyridine	methoxy pyridazine	$CH(CH_3CH_3)$	H	1	3
341	S	NH	CO	thiazole	O	tetrabutyl benzene	CO	dimethoxy pyridazine	CS	H	1	1
342	$N\text{-}SO_2$-phenyl	NH	CO	isoxazole	NH	pentyl benzene	NH	hydroxy pyrimidine	C=N-phenyl	H	1	2
343	N-methyl	NH	CO	pyrazole	O	tetrapentyl benzene	CO	thiazole	CS	H	1	3
344	N-anisolyl	CH_2	CO	isothiazole	O	methoxy benzene	CH_2	isoxazole	CO	H	2	1
345	NH	O	CO	benzene	O	dimethoxy benzene	CH_2	pyrazole	CO	H	3	1

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
346	N-pyridyl	O	CO	methyl benzene	O	trimethoxy benzene	O	isothiazole	CO	H	4	1
347	NH	N-phenyl	CO	dimethyl benzene	O	tetra methyl benzene	O	benzene	CO	H	2	2
348	NH	N-methyl	CS	trimethyl benzene	O	ethoxy benzene	S	methyl benzene	CO	H	3	2
349	NH	N	CO	tetramethyl	O	diethoxy benzene	CH_2	dimethyl benzene	CO	H	2	3
350	NH	NH	CO	ethyl benzene	O	nitro benzene	CO	trimethyl benzene	CO	H	1	3
351	NH	N-pyridyl	CO	tetraethyl benzene	O	dinitro benzene	CO	tetramethyl	CS	H	1	1
352	CH_2	NH	CO	phenyl	O	halo benzene	CO	ethyl benzene	CO	H	1	1
353	O	NH	CO	hydroxy thiophene	O	dihalo benzene	CO	tetraethyl benzene	CS	H	1	2
354	S	NH	CS	methoxy pyridazine	O	trihalo benzene	CS	propyl benzene benzene	CO	H	1	1
355	N-SO_2 phenyl	NH	CO	dimethoxy pyridazine	O	tetrahalo benzene	CH(O-phenyl)	tetra propyl benzene	CS	H	1	3
356	N-methyl	NH	CO	hydroxy pyrimidine	O	benzene carboxylic acid	CH(O-C_2H_5)	butyl benzene	CO	H	1	3
357	N-butyl	NH	CO	diamido pyrimidine	O	benzene dicarboxylic acid	CO	tetrabutyl benzene	CS	H	1	3
358	N-phenyl	NH	CO	amido pyrazine	O	amido benzene benzamide	CO	pentyl benzene	CO	H	1	3
359	N-pyridyl	NH	CO	diethoxy pyrazine	O	diamido benzene	CO	tetrapentyl benzene	CS	H	1	1

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
360	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy benzene	CO	methoxy benzene	CO	H	1	2
361	S	NH	CS	p-chloro phenyl	O	trihydroxy benzene	CS	dimethoxy benzene	CS	H	1	4
362	$N-SO_2$ phenyl	NH	CO	o-hydroxy phenyl	O	tetrahydroxy benzene	CO	trimethoxy benzene	CO	H	2	1
363	N-methyl	NH	CO	m-methoxy phenyl	O	pentahydroxy benzene	CO	tetramethyl benzene	CS	H	3	1
364	N-anisolyl	NH	CO	m-hydroxy phenyl	NH	triethoxy benzene	CO	ethoxy benzene	C=N-phenyl	H	4	1
365	N-phenyl	CH_2	CO	m-methoxy phenyl	O	tetraethoxy benzene	CO	diethoxy benzene	CO	H	2	2
366	N-pyridyl	O	CO	p-methoxy phenyl	O	pentoxy benzene	CO	nitrobenzene	CO	H	3	2
367	O	S	CO	o-hydroxy phenyl	O	dipentoxy benzene	CO	dinitro benzene	CO	H	2	3
368	CH_2	N-phenyl	CS	p-hydroxy phenyl	O	tripentoxy benzene	CS	halo benzene	CO	H	1	3
369	NH	N-methyl	CO	p-methoxy phenyl	O	tetrapentoxy benzene	CO	dihalo benzene	CS	H	1	1
370	NH	NH	CO	o-chloro phenyl	O	benzamid	CO	trihalo benzene	CO	H	1	1
371	NH	N-phenyl	CO	m-chloro phenyl	O	diamino benzene	CO	tetrahalo benzene	CO	H	1	2
372	NH	N-pyridyl	CO	p-chloro phenyl	O	methoxy pyridine	CO	benzene carboxylic acid	CO	H	1	1

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
373	CH_2	NH	CO	p-hydroxy phenyl	O	dimethoxy pyridine	CO	benzene dicarboxylic acid	CO	H	1	1
374	O	NH	CO	o-methoxy phenyl	O	hydroxy pyridine	CO	benzamide	CO	H	1	2
375	S	NH	CO	p-methoxy phenyl	O	dihydroxy pyridine	CO	benzene diamide	CO	H	1	1
376	$N\text{-}SO_2$ phenyl	NH	CO	o-hydroxy phenyl	O	dihydroxy benzene	CO	3,5-dihydroxy benzene	CS	H	1	3
377	N-methyl	NH	CO	m-methoxy phenyl	O	dihydroxy benzene	CO	trihydroxy benzene	CO	H	1	3
378	N-butyl	CH_2	CS	m-hydroxy phenyl	O	dihydroxy benzene	CS	tetrahydroxy benzene	CS	H	1	3
379	N-phenyl	O	CO	m-chloro phenyl	O	dihydroxy benzene	CO	pentahydroxy benzene	CO	H	1	3
380	N-pyridyl	O	CO	o-hydroxy phenyl	O	dihydroxy benzene	S	triethoxy benzene	CS	H	1	3
381	NH	N-phenyl	CS	o-hydroxy phenyl	O	dihydroxy benzene	CO	tetra ethoxy benzene	CO	H	1	1
382	NH	N-methyl	CO	p-methoxy phenyl	O	dihydroxy benzene	CS	pentoxy benzene	CS	H	1	2
383	NH	NH	CO	p-hydroxy phenyl	O	dihydroxy benzene	O	dipentoxy benzene	CO	H	1	4
384	NH	N-phenyl	CO	m-hydroxy phenyl	O	dihydroxy benzene	N-phenyl	tripentoxy benzene	CS	H	2	1
385	NH	N-pyridyl	CO	p-hydroxy phenyl	O	hydroxy thiophene	CO	tetrapentoxy benzene	CNH_2	H	3	1

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
386	CH_2	NH	CS	o-methoxy phenyl	O	methoxy pyridazine	CS	amino benzene	CS	H	4	1
387	O	NH	CO	o-hydroxy phenyl	O	dimethoxy pyridazine	CO	diamino benzene	$CH(CH_3CH_3)$	H	2	2
388	S	NH	CO	m-methoxy phenyl	O	hydroxy pyrimidine	N-methyl	methoxy pyridine	CS	H	3	2
389	$N\text{-}SO_2$ phenyl	NH	CO	p-chloro phenyl	NH	diamido pyrimidine	CO	dimethoxy pyridine	C=N-phenyl	H	2	3
390	N-methyl	NH	CO	p-chloro phenyl	O	amido pyrazine	N-pyridine	hydroxy pyridine	CS	H	1	3
391	N-butyl	NH	CO	p-hydroxy phenyl	NH	diethoxy pyrazine	CO	dihydroxy pyridine	CO	H	1	3
392	N-phenyl	NH	CO	p-chloro phenyl	NH	phenyl	N-purine	phenyl	CO	H	1	3
393	S	NH	CO	p-hydroxy phenyl	NH	phenyl	CO	phenyl	CO	H	1	1
394	$N\text{-}SO_2$ phenyl	NH	CS	hydroxy thiophene	NH	dihydroxy benzene	CH_2	phenyl	CO	H	1	2
395	N-methyl	NH	CO	methoxy pyridazine	CH_2	dihydroxy benzene	CH_2	phenyl	CO	H	1	4
396	N-butyl	NH	CS	dimethoxy pyridazine	O	dihydroxy benzene	O	phenyl	CO	H	2	1
397	N-phenyl	CH_2	CO	hydroxy pyrimidine	O	dihydroxy benzene	O	phenyl	CO	H	3	1
398	N-pyridyl	O	CS	diamido pyrimidine	N-phenyl	dihydroxy benzene	S	phenyl	CS	H	4	1
399	O	O	CO	amido pyrazine	N-methyl	dihydroxy benzene	CH_2	phenyl	CO	H	2	2

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
400	CH_2	N-phenyl	CO	diethoxy pyrazine	NH	dihydroxy benzene	CO	phenyl	CO	H	3	2
401	NH	N-methyl	CO	dihydroxy benzene	N-phenyl	phenyl	CO	dihydroxy benzene	CO	H	2	3
402	NH	NH	CO	dihydroxy benzene	N-methyl pyridyl	phenyl	CO	dihydroxy benzene	CO	H	1	3
403	NH	N-phenyl	CS	dihydroxy benzene	NH	phenyl	CO	dihydroxy benzene	CO	H	1	1
404	NH	N-pyridyl	CO	dihydroxy benzene	NH	dihydroxy benzene	CS	phenyl	CS	H	1	1
405	CH_2	NH	CO	phenyl	NH	dihydroxy benzene	CH(O-phenyl)	phenyl	CO	H	1	2
406	O	NH	CS	phenyl	NH	dihydroxy benzene	CH(O-C_2H_5)	phenyl	CO	H	1	1
407	S	NH	CO	pyridine	NH	butyl benzene	CO	methoxy pyridine	CS	H	1	2
408	N-SO_2 phenyl	NH	CS	pyrrole	CH_2	tetrabutyl benzene	CO	dimethoxy pyridine	CO	H	1	2
409	N-methyl	NH	CO	oxazole	O	pentyl benzene	CO	hydroxy pyridine	CS	H	1	1
410	N-butyl	CH_2	CS	indole	O	tetrapentyl benzene	CO	dihydroxy pyridine	CO	H	1	2
411	N-phenyl	O	CO	purine	N-phenyl	methoxy benzene	CS	ethoxy pyrrole	CS	H	1	1
412	N-methyl pyridyl	O	CS	furan	N-methyl	dimethoxy benzene	CO	dihydroxy pyrrole	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
413	NH	N-phenyl	CO	thiophene	NH	trimethoxy benzene	CO	dimethoxy indole	CS	H	1	3
414	NH	N-methyl	CS	pyridazine	N-phenyl	tetra methyl benzene	CO	hydroxy purine	CO	H	1	3
415	NH	NH	CO	pyrimidine	N-pyridyl	ethoxy benzene	CO	furan.	CS	H	1	3
416	NH	N-phenyl	CS	pyrazine	NH	diethoxy benzene	CS	hydroxy thiophene	CO	H	1	1
417	NH	N-pyridyl	CO	imidazole	NH	nitro benzene	CO	methoxy pyridazine	CS	H	1	2
418	CH_2	NH	CS	thiazole	NH	dinitro benzene	S	dimethoxy pyridazine	CO	H	1	4
419	O	NH	CO	isoxazole	NH	halo benzene	CO	hydroxy pyrimidine	CS	H	2	1
420	S	NH	CS	pyrazole	NH	dihalo benzene	CS	diamido pyrimidine	CO	H	3	1
421	N-SO_2 phenyl	NH	CO	isothiazole	NH	trihalo benzene	O	amido pyrazine	CS	H	4	1
422	N-methyl	NH	CO	benzene	NH	tetrahalo benzene	N-phenyl	pyridine	CO	H	2	2
423	N-butyl	NH	CO	methyl benzene	NH	carboxy acid benzene	CO	pyrrole	CO	H	3	2
424	N-phenyl	NH	CO	dimethyl benzene	NH	benzene dicarboxylic acid	CS	oxazole	CO	H	2	3
425	N-pyridyl	NH	CO	trimethyl benzene	NH	benzamide	CO	indole	CS	H	1	3
426	S.	NH	CO	tetramethyl	NH	benzene diamide	N-methyl	purine	CO	H	1	1

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
427	N-SO 2 phenyl	NH	CO	ethyl benzene	NH	3,5-dihydroxy benzene	CO	furan	CS	H	1	1
428	N-methyl	NH	CS	tetraethyl benzene	NH	trihydroxy benzene	N-pyridine	thiophene	CO	H	1	2
429	N-butyl	NH	CO	propyl benzene benzene	CH_2	tetrahydroxy benzene	CO	pyridazine	CS	H	1	1
430	N-phenyl	CH_2	CO	tetra propyl benzene	O	pentahydroxy benzene	N-purine	pyrimidine	CO	H	1	3
431	N-pyridyl	O	CO	butyl benzene	O	triethoxy benzene	CO	pyrazine	CO	H	1	3
432	O	O	CO	tetrabutyl benzene	N-phenyl	tetra ethoxy benzene	CH_2	imidazole	CS	H	1	3
433	CH_2	N-phenyl	CO	pentyl benzene	N-methyl	pentoxy benzene	CH_2	thiazole	CO	H	1	3
434	NH	N-methyl	CS	tetrapentyl benzene	NH	dipentoxy benzene	O	isoxazole	CS	H	1	1
435	NH	NH	CO	methoxy benzene	N-phenyl	tripentoxy benzene	O	pyrazole	CO	H	1	2
436	NH	N-phenyl	CO	dimethoxy benzene	N-pyridyl	tetrapentoxy benzene	S	isothiazole	CS	H	1	4
437	NH	N-pyridyl	CO	trimethoxy benzene	NH	aniline	CH_2	benzene	CO	H	2	1
438	CH_2	NH	CO	tetra methyl benzene	NH	diamino benzene	CO	pyrazole	CS	H	3	1
439	O	NH	CO	ethoxy benzene	NH	pyridine	CO	isothiazole	CO	H	4	1
440	S	NH	CO	diethoxy benzene	NH	pyrrole	CO	benzene	CS	H	2	2

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
441	N-SO_2 phenyl	NH	CS	nitrobenzene	NH	oxazole	CO	phenyl	C=NH	H	3	2
442	N-methyl	NH	CO	dinitrobenzene	CH_2	indole	CS	phenyl	CS	H	2	3
443	N-butyl	N-methyl	CO	halo benzene	O	purine	CH(O-phenyl)	phenyl	$CH(CH_3CH_3)$	H	1	3
444	N-phenyl	O	CO	dihalo benzene	N-methyl	furan	$CH(O-C_2H_5)$	phenyl	CS	H	1	1
445	N-pyridyl	O	CO	trihalo benzene	N-phenyl	thiophene	CO	phenyl	C=N-phenyl	H	1	1
446	NH	N-phenyl	CO	tetrahalo benzene	N-methyl	pyridazine	CS	phenyl	CS	H	1	2
447	NH	N-methyl	CO	benzene carboxylic acid	NH	pyrimidine	CO	phenyl	CO	H	1	1
448	NH	N-butyl	CS	benzene dicarboxylic acid	N-phenyl	pyrazine	S	phenyl	CO	H	1	1
449	NH	N-phenyl	CO	benzamide	N-pyridyl	imidazole	CO	phenyl	CO	H	1	2
450	NH	N-pyridyl	CO	benzene diamide	NH	thiazole	CS	phenyl	CO	H	1	1
451	CH_2	NH	CO	3,5-dihydroxy benzene	NH	isoxazole	O	phenyl	CO	H	1	3
452	O	NH	CO	trihydroxy benzene	NH	pyrazole	N-phenyl	phenyl	CO	H	1	3
453	S	NH	CO	tetrahydroxy benzene	NH	isothiazole	CO	phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
454	N-SO_2-phenyl	NH	CO	pentahydroxy benzene	NH	benzene	CS	dihydroxy benzene	CS	H	1	3
455	N-methyl	NH	CO	triethoxy benzene	NH	phenyl	N-methyl	dihydroxy benzene	CO	H	1	3
456	N-butyl	NH	CO	tetra ethoxy benzene	O	phenyl	N-methyl	dihydroxy benzene	CO	H	1	1
457	N-phenyl	NH	CO	pentoxy benzene	O	phenyl	CO	dihydroxy benzene	CO	H	1	2
458	N-pyridyl	NH	CS	dipentoxy benzene	O	phenyl	N-ethyl	dihydroxy benzene	CO	H	1	4
459	NH	NH	CO	tripentoxy benzene	O	phenyl	CO	dihydroxy benzene	CS	H	2	1
460	S	NH	CO	tetrapentoxy benzene	O	phenyl	N-purine	dihydroxy benzene	CO	H	3	1
461	N-SO_2-phenyl	NH	CS	aniline	O	phenyl	CO	dihydroxy benzene	CO	H	4	1
462	N-methyl	NH	CO	diamino benzene	O	phenyl	CH_2	dihydroxy benzene	CS	H	2	2
463	N-butyl	NH	CO	methoxy pyridine	O	phenyl	CH_2	dihydroxy benzene	CO	H	3	2
464	N-phenyl	CH_2	CO	dimethoxy pyridine	O	phenyl	O	dihydroxy benzene	CO	H	2	3
465	N-pyridyl	O	CO	hydroxy pyridine	O	phenyl	O	dihydroxy benzene	CO	H	1	3
466	O	O	CS	dihydroxy pyridine	O	phenyl	S	dihydroxy benzene	CO	H	1	1
467	CH_2	N-phenyl	CO	ethoxy pyrrole	O	phenyl	CH_2	dihydroxy benzene	CS	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
468	NH	N-methyl	CO	dihydroxy pyrrole	O	pyrazole	CO	dihydroxy benzene	CO	H	1	3
469	NH	N-butyl	CO	dimethoxy indole	O	isothiazole	CO	dihydroxy benzene	CO	H	1	1
470	NH	N-phenyl	CO	hydroxy purine	O	benzene	CO	dihydroxy benzene	CO	H	1	2
471	NH	N-pyridyl	CO	demethoxy furan	O	methyl benzene	CO	dihydroxy benzene	CO	H	1	4
472	CH_2	NH	CO	hydroxy thiophene	O	dimethyl benzene	CS	dihydroxy benzene	CO	H	2	1
473	O	NH	CO	methoxy pyridazine	O	trimethyl benzene	CH(O-phenyl)	dihydroxy benzene	CO	H	3	1
474	S	NH	CS	dimethoxy pyridazine	O	tetramethyl	CH(O-C_2H_5)	dihydroxy benzene	CO	H	4	1
475	N-SO_2 phenyl	NH	CO	hydroxy pyrimidine	O	ethyl benzene	CO	pyrazole	CS	H	2	2
476	N-methyl	NH	CS	diamido pyrimidine	O	tetraethyl benzene	CO	isothiazole	CO	H	3	2
477	N-butyl	CH_2	CO	amido pyrazine	O	propyl benzene benzene	CO	benzene	CO	H	2	3
478	N-phenyl	O	CS	pyrazole	O	tetra propyl benzene	CO	methyl benzene	CS	H	1	3
479	N-pyridyl	O	CO	isothiazole	N-phenyl	butyl benzene	CS	dimethyl benzene	CO	H	1	1
480	NH	N-phenyl	CO	benzene	N-methyl	tetrabutyl benzene	CO	trimethyl benzene	CO	H	1	1

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
481	NH	N-methyl	CO	p-hydroxy phenyl	N-butyl	pentyl benzene	S	tetramethyl	CS	H	1	2
482	NH	N	CO	m-methoxy phenyl	N-phenyl	tetrapentyl benzene	CO	diamino benzene	CO	H	1	1
483	NH	N-phenyl	CO	p-methoxy phenyl	N-pyridyl	methoxy benzene	CS	methoxy pyridine	CS	H	1	2
484	NH	N-pyridyl	CS	p-hydroxy phenyl	NH	dimethoxy benzene	O	dimethoxy pyridine	CO	H	1	2
485	CH_2	NH	CO	o-hydroxy phenyl	NH	trimethoxy benzene	N-phenyl	hydroxy pyridine	CS	H	1	1
486	O	NH	CS	o-chloro phenyl	NH	tetra methyl benzene	CO	dihydroxy pyridine	CO	H	1	2
487	S	NH	CO	m-hydroxy phenyl	NH	phenyl	CS	ethoxy pyrrole	CS	H	1	1
488	N-SO_2 phenyl	NH	CS	m-methoxy phenyl	NH	phenyl	CO	dihydroxy pyrrole	CO	H	1	3
489	N-methyl	NH	CO	p-hydroxy phenyl	CH_2	phenyl	N-methyl	dimethoxy indole	CS	H	1	3
490	N-butyl	NH	CS	p-chloro phenyl	NH	phenyl	CO	hydroxy purine	C=NH	H	1	3
491	N-phenyl	NH	CO	p-methoxy phenyl	O	phenyl	N-butyl	demethoxy furan	CS	H	1	3
492	N-pyridyl	NH	CS	o-methoxy phenyl	N-phenyl	phenyl	CO	hydroxy thiophene	$CH(CH_3CH_3)$	H	1	1
493	NH	NH	CO	o-chloro phenyl	N-methyl	phenyl	N-methyl	methoxy pyridazine	CS	H	1	2
494	S	NH	CS	dihydroxy benzene	NH	dihydroxy benzene	CO	dimethoxy pyridazine	C=N-phenyl	H	1	4

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	m	n
495	N-SO_2 phenyl	NH	CO	dihydroxy benzene	N-phenyl	dihydroxy benzene	CH_2	hydroxy pyrimidine	CS	H	2	1
496	N-methyl	NH	CS	dihydroxy benzene	O	dihydroxy benzene	CH_2	diamido pyrimidine	CO	H	3	1
497	N-butyl	NH	CO	dihydroxy benzene	N-phenyl	dihydroxy benzene	O	methoxy benzene	CO	H	4	1
498	N-phenyl	CH_2	CO	dihydroxy benzene	N-methoxy	phenyl	O	dimethoxy benzene	CO	H	2	2
499	N-pyridyl	O	CO	dihydroxy benzene	NH	phenyl	S	trimethoxy benzene	CO	H	3	2
500	O	O	CO	dihydroxy benzene	N-phenyl	phenyl	CH_2	tetra methyl benzene	CO	H	2	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
501	NSO_2CH_3	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
502	NSO_2 phenyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
503	NSO_2CH_3	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-ethyoxycarboxy-6-hydroxy phenyl	CO	H	1	1
504	NSO_2CH_3	NH	CO	p-hydroxy phenyl	O	3-ethoxy-5-hydroxy phenyl	CO	2-ethoxycarboxy-6-hydroxy phenyl	CO	H	1	1
505	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-hydroxy phenyl	CO	H	1	3
506	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-hydroxy phenyl	CO	H	1	3
507	CH_2	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2benzyloxycarbonyl phenyl	CO	H	1	3
508	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
509	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
510	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
511	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-hydroxy naphthyl	CO	H	1	3
512	NCONH-phenyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
513	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2,3,5,6-tetramethyl phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
514	NH	NH	CO	p-hydroxy phenyl	O	3,5-dimethoxy phenyl	CO	2,6-dihydroxy phenyl	CO	H	1	3
515	NH	NH	CO	p-hydroxy phenyl	NH	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
516	NH	NH	CO	p-hydroxy phenyl	NH	3,5-dimethoxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
517	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
518	NH	NH	CO	p-hydroxy phenyl	O	3,5-dimethoxy phenyl	CO	2,6-dimethoxy phenyl	CO	H	1	3
519	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2,6-dimethoxy phenyl	CO	H	1	3
520	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy cyclohexane	CO	H	1	3
521	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2,6-dihydroxy phenyl	CO	H	1	3
522	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	1-hydroxy-2-naphthyl	CO	H	1	3
523	NCH_2 phenyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
524	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2,6-dichloro phenyl	CO	H	1	3
525	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy cyclohexane	CO	H	1	3
526	NH	NH	SO_2	p-methyl phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
527	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-methoxy-6-hydroxy phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
528	NH	NH	CO	p-hydroxy phenyl	O	3-benzoyloxy-5-hydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
529	NCO phenyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
530	NCO phenyl	NH	CO	p-hydroxy phenyl	O	3-benzoyloxy-5-hydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
531	NCO phenyl	NH	CO	p-benzoate phenyl	O	3-hydroxy-5-benzoate phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
535	NCH_2 phenyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	3-hydroxy phthalido		CO	H	1	3
536	NH	NH	CO	p-carboxy phenyl	O	3,5-dihydroxy phenyl	CO	2,6-dihydroxy phenyl	CO	H	1	3
537	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-3-pyridine	CO	H	1	3
538	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
539	NCH_3	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
541	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	3-carboxy-2-pyridine	CO	H	1	3
542	NH	NCH_3	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
543	NH	NH	CO	p-hydroxy phenyl	NCH_3	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
544	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	phenyl	CO	H	1	3

Cmpd. ∅	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
545	CH_2	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	phenyl	CO	H	1	2
546	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	3,4-dibenzyloxy-phenylcarbonyl phenyl	CO	H	1	3
547	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	3,4-dihydroxy phenyl	CO	H	1	3
548	NH	NH	CO	4-(2-hydroxy-phenylcarbonyl)-3,5-dihydroxy phenyl	O	phenyl	OH		CO	H	1	3
549	NCH-$(CH_3)_2$	NH	CO	4-(2-hydroxy-phenylcarbonyl)-3,5-dihydroxy phenyl	O	phenyl	OH		CO	H	1	3
550	NH	NH	CO	p-hydroxy phenyl	NH	3,5-dihydroxy phenyl	CO	2-hydroxy phenyl	CO	H	1	3
551	NH	NH	CO	p-hydroxy phenyl	NH	3,5-dihydroxy phenyl	CO	2-hydroxy phenyl	CO	H	1	3
552	NH	NH	CO	p-amino phenyl	O	3,5-dihydroxy phenyl	CO	2-hydroxy phenyl	CO	H	1	3
553	NH	NH	CO	4-fluoro phenyl	O	3,5-dihydroxy phenyl	CO	2-hydroxy phenyl	CO	H	1	3
554	S	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
555	SO_2	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
556	NH	NH	CO	p-hydroxy phenyl	O	phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
557	O	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
558	$NCOCH_3$	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
559	NH	NH	CO	p-hydroxy phenyl	O	phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
560	$NCOCF_3$	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
562	NSO_2 phenyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
563	NH	NH	CO	p-hydroxy phenyl	NH	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
566	CH_2	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-methoxycarbonyl-6-hydroxy phenyl	CO	H	1	3
567	O	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-methoxycarbonyl-6-hydroxy phenyl	CO	H	1	3
568	NH	NH	CO	p-hydroxy phenyl	NH	3,5-dihydroxy phenyl	CO	2-methoxycarbonyl-6-hydroxy phenyl	CO	H	1	3
569	NSO_2(5-dimethyl-amino-1-naphtha-lene)	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
570	NSO_2-1-naphtha-lene	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
571	NSO_2-2-naphtha-lene	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
572	NSO_2-2-methyl-5-nitro phenyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
573	NSO_2-2-nitro phenyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
574	NSO_2-4-nitro phenyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
575	NCH=NC-$(CH_3)_3$	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
576	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-butoxycarbonyl-6-hydroxy phenyl	CO	H	1	1
577	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-(2-methyl-propyloxy)-carbonyl-6-hydroxy phenyl	CO	H	1	1
578	CH_2	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-nitrilo-6-hydroxy phenyl	CO	H	1	1
579	NCONH phenyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
580	NCONH-CH_3	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-methoxycarbonyl-6-hydroxy phenyl	CO	H	1	1
581	NCONH phenyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-methoxycarbonyl-6-hydroxy phenyl	CO	H	1	3
582	CH_2	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-hydroxy phenyl	CO	H	1	3
583	CH_2	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
584	NH	NH	CO	p-hydroxy phenyl	NH	3,5-dihydroxy phenyl	CO	3,4-dihydroxy phenyl	CO	H	1	3
585	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy phenyl	CO	H	1	1
586	NCH_2 phenyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-hydroxy phenyl	CO	H	1	3
587	NCH_2 phenyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-hydroxy phenyl	CO	H	1	3
588	CH_2	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
589	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
590	NCO-$(CH_2)_{14}$-CH_3	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
591	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-hydroxy-1-naphthyl	CO	H	1	1
592	NCH-$(CH_3)_2$	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
593	NCONH phenyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
594	NCONH-CH_3	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
595	$NCOOCH_2$-$CH(CH_3)_2$	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
596	$NCOCF_3$	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-(4-acetoxy-benzyloxycarbonyl)-6-hydroxy phenyl	CO	H	1	1

Cmpd. ∅	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
597	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	CH_3	1	3
598	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	CH_3	1	3
599	NSO_2CH_3	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-hydroxy-1-naphthalene	CO	H	1	1
600	NSO_2CH_3	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	1
601	NSO_2 phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	1
602	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	3
603	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dimethoxy phenyl	CO	2,6-dibenzyloxy phenyl	CO	H	1	3
604	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dimethoxy phenyl	CO	2,6-dimethoxy phenyl	CO	H	1	3
605	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2,6-dimethoxy phenyl	CO	H	1	3
606	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl cyclohexane	CO	H	1	3
607	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	1-benzyloxy-2-naphthyl	CO	H	1	3
608	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2,6-dichloro phenyl	CO	H	1	3
609	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl cyclohexane	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
610	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	3
611	NCH_2 phenyl	NH	SO_2	p-methyl phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	3
612	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxy-6-benzyloxycarbonyl phenyl	CO	H	1	3
613	NCH_2 phenyl	NH	CO	p-hydroxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-methoxy-6-benzyloxy phenyl	CO	H	1	3
614	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	NH	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	3
615	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	NH	3,5-dibenzyloxy phenyl	CO	2-benzylcarboxy-6-benzyloxy phenyl	CO	H	1	3
617	NCH_2 phenyl	NH	CO	p-benzyloxycar-bonyl phenyl	O	3,5-dibenzyloxy phenyl	CO	2,6-dibenzyloxy phenyl	CO	H	1	3
618	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-3-pyridinyl	CO	H	1	3
619	NCH_2 phenyl	NH	CO	5-Indole	O	3,5-dibenzyloxy phenyl	CO	2- benzyloxy carbonyl-6-benzyloxyphenyl	CO	H	1	3
620	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	NCH_3	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	3
622	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	3-benzyloxycar-bonyl-2-pyridinyl	CO	H	1	3
623	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	O	phenyl	CH_2	H	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
636	$NCOCH_3$	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	1
637	$NCOCF_3$	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	1
640	$NCOOCH_2$ phenyl	NH	CO	p-benzyloxy phenyl	NH	3,5-dibenzyloxy phenyl	CO	2-benzyl oxycarbonyl-6-benzyloxy phenyl	CO	H	1	1
642	NCH=NC-$(CH_3)_3$	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxy carbonyl-6-benzyloxyphenyl	CO	H	1	1
643	NCOOC-$(CH_3)_3$	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	1
644	NCOOC-$(CH_3)_3$	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
645	NCOOC-$(CH_3)_3$	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-butoxycarbonyl-6-hydroxy phenyl	CO	H	1	1
646	NCOOC-$(CH_3)_3$	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-(2-methyl-propyloxycar-bonyl)-6-hydroxy phenyl	CO	H	1	1
647	CH_2	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-nitrilo-6-benzyloxy phenyl	CO	H	1	1
648	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	NH	3,5-dibenzyloxy phenyl	CO	3,4-dibenzyloxy phenyl	CO	H	1	3
649	$NCOOCH_2$ phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl phenyl	CO	H	1	1

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
624	NCH_2 phenyl	NCH_3	CO	p-benzyloxy phenyl	O	phenyl	CH_2	H	CO	H	1	3
625	NCH_2 phenyl	NCH_3	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	3
626	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	NCH_3	3,5-dibenzyloxy phenyl	CO	2-benzyloxy carbonyl-6-benzyloxy phenyl	CO	H	1	3
627	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	phenyl	CO	H	1	3
628	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	NH	3,5-dibenzyloxy phenyl	CO	2-benzyloxy phenyl	CO	H	1	3
629	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	NH	3,5-dibenzyloxy phenyl	CO	2-benzyloxy phenyl	CO	H	1	3
630	NCH_2 phenyl	NH	CO	p-nitro phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxy phenyl	CO	H	1	3
631	NCH_2 phenyl	NH	CO	p-fluoro phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxy phenyl	CO	H	1	3
632	S	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	3
633	SO_2	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	3
634	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	O	phenyl	CO	2-benzyl oxycarbonyl-6-benzyloxy phenyl	CO	H	1	3
635	O	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
650	NCH_2 phenyl	NH	CO	phenyl	O	3,5-dibenzyloxy phenyl	CO	3,4-dibenzyloxy phenyl	CO	H	1	3
651	CH_2	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	3
652	$NCOOCH_2$ phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	1
653	$NCOOCH_2$ phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxy-1-naphthyl	CO	H	1	1
654	NCH-$(CH_3)_2$	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	1
655	NCONH phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	1
656	NCONH-CH_3	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	1
657	$NCOOCH_2$ $CH(CH_3)_2$	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	1
658	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	CH_3	1	3
659	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	CH_3	1	3
660	NSO_2CH_3	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxy-1-naphthyl	CO	H	1	1

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
661	NCH_2 phenyl	NH	CO	phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	3
662	$N(CH_2)_4$ OH	NH	CO	phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
663	NCH_2 phenyl	NH	CO	p-methyl phenyl	O	3,5-dibenzyloxy phenyl	CO	2-methoxy-6-benzyloxy phenyl	CO	H	1	3
664	NH	NH	CO	p-methyl phenyl	O	3,5-dihydroxy phenyl	CO	2-methoxy-6-hydroxy phenyl	CO	H	1	3
665	NCH_2 phenyl	NH	CO	p-methoxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	3
666	NH	NH	CO	p-methoxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
667	NCH_2 phenyl	NH	CO	o-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	3
668	NH	NH	CO	o-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
669	NCH_2 phenyl	NH	CO	p-fluoro phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	3
670	NH	NH	CO	p-fluoro phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
671	NCH_2 phenyl	NH	CO	5-benzyloxy-2-indole	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	3
672	NH	NH	CO	5-hydroxy-2-indole	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
673	NCH_2 phenyl	NH	CO	p-benzyloxycar-bonyl phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	3
674	NH	NH	CO	p-carboxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
675	NH	NH	CO	3,4-dihydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
676	NSO_2CH_3	NH	CO	p-benzyloxy phenyl	NH	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	1
677	NSO_2CH_3	NH	CO	p-hydroxy phenyl	NH	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
678	$NP{=}O(OCH_2CH_3)_2$	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	1
679	$NP{=}O(OCH_2CH_3)_2$	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
680	CH_2	NH	CO	2-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	1
681	CH_2	NH	CO	2-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
682	CH_2	NH	CO	2-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-methoxycarbonyl-6-hydroxy phenyl	CO	H	1	1
683	CH_2	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	6-benzyloxy-2-tetrazolyl phenyl	CO	H	1	1
684	CH_2	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	6-hydroxy-2-tetrazolyl phenyl	CO	H	1	1

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
685	CH_2	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	6-hydroxy-2-(2-methyltetrazolyl) phenyl	CO	H	1	1
686	CH_2	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	6-hydroxy-2-(3-methyltetrazolyl) phenyl	CO	H	1	1
687	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-hydroxy-1-(5,6,7,8-tetrahydro) naphthyl	CO	H	1	1
688	NCOOC-$(CH_3)_3$	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-hydroxy-1-(5,6,7,8-tetrahydro) naphthyl	CO	H	1	1
689	NCOOC-$(CH_3)_3$	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-hydroxy-1-naphthyl	CO	H	1	1
690	NCOOC-$(CH_3)_3$	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxy-1-naphthyl	CO	H	1	1
691	NH	NH	CO	p-$NHSO_2CH_3$ phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
692	NH	NH	CO	p-NH_2 phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
693	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	3-benzyloxycar-bonyl-4-benzyloxy phenyl	CO	H	1	3
694	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	3-carboxy-4-hydroxy phenyl	CO	H	1	3
695	$NCOOCH_2$ phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	2

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
696	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	2
697	NCH_2CH_3	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	2
698	$NCOOCH_2$ phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	2
699	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-hydroxy phenyl	CH_2	H	1	3
700	NCOOC-$(CH_3)_3$	NH	CO	p-methoxy-methyleneoxy phenyl	O	3,5-dimethoxy-methyleneoxy phenyl	CO	2-methoxy-methyleneoxy phenyl	CH_2	H	1	3
701	$NCOOCH_2$ phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	2	1
702	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	2	1
703	$NCOOCH_2$ phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	2	1
704	NCH_2CH_3	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	2	1
705	$NCOOCH_2$ phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-ethoxycarbonyl-6-benzyloxy phenyl	CO	H	1	1
706	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-ethoxycarbonyl-6-hydroxy phenyl	CO	H	1	1
707	CH_2	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycar-bonyl-6-benzyloxy phenyl	CO	H	1	1

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
708	CH_2	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
709	$NCOOCH_2$ phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycarbonyl-1-naphthyl	CO	H	1	1
710	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-1-naphthyl	CO	H	1	1
711	NCOOC-$(CH_3)_3$	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
712	$NCOOCH_3$	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-methoxycarbonyl-6-hydroxy phenyl	CO	H	1	1
713	$NCOOCH_3$	NH	CO	p-hydroxy phenyl	O	3-methoxycarbonyloxy-5-hydroxy phenyl	CO	2-methoxycarbonyl-6-hydroxy phenyl	CO	H	1	1
714	CH_2	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-ethoxycarbonyl-6-hydroxy phenyl	CO	H	1	1
715	CH_2	NH	CO	p-hydroxy phenyl	O	3-ethoxy-5-hydroxy phenyl	CO	2-ethoxycarbonyl-6-hydroxy phenyl	CO	H	1	1
716	$NCOOCH_3$	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
717	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-methoxycarbonyl-6-hydroxy phenyl	CO	H	1	1
718	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
719	NSO_2CH_3	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-methoxycarbonyl-6-hydroxy phenyl	CO	H	1	3
720	NCH_2 phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxy-6-methyl phenyl	CO	H	1	1

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
721	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-methyl-6-hydroxy phenyl	CO	H	1	1
722	$NCOOCH_2$ phenyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
723	CH_2	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-methoxycarbonyl-6-hydroxy phenyl	CO	H	1	1
724	NSO_2CH_2 phenyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
725	$NCOOCH_2$ phenyl	NH	CO	p-acetoxy phenyl	O	3-acetoxy-5-hydroxy phenyl	CO	2-acetoxy-6-ethoxycarbonyl phenyl	CO	H	1	1
726	NH	NH	CO	p-acetoxy phenyl	O	3-acetoxy-5-hydroxy phenyl	CO	2-acetoxy-6-ethoxycarbonyl phenyl	CO	H	1	1
727	NH	NH	CO	p-hydroxy phenyl	O	3-butoxy-5-hydroxy phenyl	CO	2-butoxycarbonyl-6-hydroxy phenyl	CO	H	1	1
728	CH_2	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CH_2	H	1	1
729	CH_2	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-methoxycarbonyl-6-hydroxy phenyl	CH_2	H	1	1
730	$N(CH_2)_4OH$	NH	CO	p-carboxy phenyl	O	3,5-dihydroxy phenyl	CO	2,6-dihydroxy phenyl	CO	H	1	3
731	NH	NH	CO	p-carboxy phenyl	O	3,5-dihydroxy phenyl	CO	2,6-dihydroxy phenyl	CO	H	1	3
732	NH	NH	CO	p-methyl phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
733	NCH_2 phenyl	NH	CO	p-methyl phenyl	O	3,5-dibenzyloxy phenyl	CO	2-benzyloxycarbonyl-6-benzyloxy phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
734	$NCOOCH_2$ phenyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
735	NCOOC-$(CH_3)_3$	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-cyclohexylmeth-oxycarbonyl-6-hydroxy phenyl	CO	H	1	1
736	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-cyclohexylmeth-oxycarbonyl-6-hydroxy phenyl	CO	H	1	1
737	$NCOOCH_2$ phenyl	NH	CO	p-benzyloxy phenyl	NH	3,5-dibenzyloxy phenyl	CO	2-carboxy-6-benzyloxy phenyl	CO	H	1	1
738	$NCOOCH_2$ phenyl	NH	CO	p-benzyloxy phenyl	NH	3,5-dibenzyloxy phenyl	CO	2-methoxycarbonyl-6-benzyloxy phenyl	CO	H	1	1
739	NH	NH	CO	p-hydroxy phenyl	NH	3,5-dihydroxy phenyl	CO	2-methoxycarbonyl-6-hydroxy phenyl	CO	H	1	1
740	NCH-$(CH_3)_2$	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-methoxycarbonyl-6-hydroxy phenyl	CO	H	1	1
741	$NCOOCH_2$ phenyl	NH	CO	p-hydroxy phenyl	O	3-hexanoyloxy-5-hydroxy phenyl	CO	2-hexanoyloxy-6-carboxy phenyl	CO	H	1	1
742	NH	NH	CO	p-hydroxy phenyl	O	3-hexanoyloxy-5-hydroxy phenyl	CO	2-hexanoyloxy-6-carboxy phenyl	CO	H	1	1
743	NCOOC-$(CH_3)_3$	NH	CO	p-hydroxy phenyl	O	3-butoxy-5-hydroxy phenyl	CO	2-butoxycarbonyl-6-hydroxy phenyl	CO	H	1	1
744	NSO_2-(4-N-methyl acetamido phenyl)	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
745	NSO_2(4-N-methyl acetamido phenyl)	NH	CO	4-(4-N-methylacet-amidobenzene sulfonyloxy) phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
746	NSO_2(4-N-methyl acetamido phenyl)	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
747	NSO_2(4-N-methyl acetamido phenyl)	NH	CO	4-(4-acetamido)-sulfonyloxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
748	NSO_2 phenyl	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-ethoxycarbonyl-6-benzyloxyphenyl	CO	H	1	1
749	NSO_2 phenyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-ethoxycarbonyl-6-hydroxyphenyl	O	H	1	1
750	N-(4-acet-amido)-3-chloro-benzene sulfonyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
751	N-2-acet-amido-4-methyl-5-thiazolyl-sulfonyl	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	3
752	$NCOOCH_2$ phenyl	NH	CO	p-benzyloxy phenyl	O	5-methoxy-methyleneoxy-3-decyloxy phenyl	CO	6-formyl-2-methoxymethylene oxyphenyl	CO	H	1	1

Cmpd. #	A	B_1	B_2	Z	D	E	F	G	X	K	M	N
753	$NCOOCH_2$ phenyl	NH	CO	p-benzyloxy phenyl	O	3-hydroxy-4-decyloxy phenyl	CO	2-formyl-6-hydroxy phenyl	CO	H	1	1
754	$NCOOCH_2$ phenyl	NH	CO	p-benzyloxy phenyl	O	3-hydroxy-4-decyloxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
755	$NCOOCH_2$ phenyl	NH	CO	p-hydroxy phenyl	O	3-hydroxy-4-benzyloxy phenyl	CO	2-carboxy-6-hydroxy phenyl	CO	H	1	1
756	NH	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CH_2	2-carboxy-6-hydroxy phenyl	CO	H	1	3
757	CH_2	NH	CO	p-benzyloxy phenyl	O	3,5-dibenzyloxy phenyl	CO	2-trifluoromethane-sulfonamino-6-benzyloxy phenyl	CO	H	1	1
758	CH_2	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-trifluoromethane-sulfonamino-6-hydroxy phenyl	CO	H	1	1
759	CH_2	NH	CO	p-hydroxy phenyl	O	3,5-dihydroxy phenyl	CO	2-[1,1-dimethyleth oxymethyleneoxy]-6-hydroxyphenyl	CO	H	1	1

The following, nonlimiting Examples illustrate preferred methods for preparing the compounds for use in the method of the present invention and the data demonstrating PKC inhibitory activity of the Compounds used in the present invention.

EXAMPLES

3-Acetylaminohexahydro-1-phenylmethylazepin-2,4-dione

A solution of hexahydro-1-phenylazepin-2,3,4-trione-3-oxime (1.23 g, 5mmol) in 4:1 acetic acid/acetic anhydride (20 ml) was treated with Raney nickel (Aldrich, one-half tsp) in a Parr bottle and subjected to hydrogenation for eighteen hours at 40-45 psi and room temperature. The mixture was carefully evacuated of hydrogen and filtered through Celite®. The filter pad was then washed with methanol (with care taken not to let the filter pad become dry). The filtrate was concentrated *in vacuo* and the residue was diluted with toluene and further concentrated to remove most of the acetic acid. The residue was chilled on an ice bath and treated with saturated sodium bicarbonate carefully to avoid excessive bubbling. The cloudy aqueous solution was extracted with methylene chloride (3 x 50 ml), and the combined organic solution was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was flash chromatographed on silica gel (eluted with 19:1 methylene chloride/methanol) to afford 3-acetylaminohexahydro-1-phenylmethylazepin-2,4-dione (1.11 g, 81%) as a white solid.

syn-3-Aminohexahydro-4-hydroxy-1-phenylmethylazepin-2-one

A solution of 3-acetylaminohexahydro-1-phenylmethylazepin-2,4-dione (0.82 g, 3.0 mmol) in absolute ethanol (15 ml) was treated with sodium borohydride (0.23 g, 6 mmol) and stirred for thirty minutes. The solution was then treated with water (5 ml) and concentrated *in vacuo*, and taken up in 2:1 ethanol/water (7.5 ml). Concentrated hydrochloric acid (2.5 ml) was added, and the mixture was refluxed for two hours and partially concentrated, then diluted with water (25 ml). The aqueous acidic mixture was extracted with ether (25

ml), and the aqueous solution was basified with 30% sodium hydroxide and extracted with methylene chloride (3 x 40 ml). The combined methylene chloride extracts were washed with water (25 ml), dried (Na_2SO_4), and concentrated *in vacuo*, to a yellow solid, which was recrystallized from ethyl acetate to afford *syn*-3-aminohexahydro-4-hydroxy-1-phenylmethylazepin-2-one (0.42 g, 60%) as a white solid.

syn-3-Aminohexahydro-4-hydroxy-1-phenylmethylazepine

A cooled (5°C) solution of lithium aluminum hydride/tetrahydrofuran (Aldrich, 1.0. N, 5.1 ml) under nitrogen was treated with *syn*-3-aminohexahydro-4-hydroxy-1-phenlmethylazepin-2-one (0.40 g, 1.7 mmol) in portions so that the pot temperature did not exceed 15°C. The mixture was refluxed for 6.5 hours, cooled on an ice bath, and carefully treated with water (0.21 ml), 15% sodium hydroxide (0.21 ml), and water (0.63 ml). The suspension was allowed to stir for five days, during which time the product partially decomposed (optimal time is 2-5 hours). The suspension was filtered, and the filtrate was concentrated *in vacuo* and chromatographed on silica gel (eluted with 90:8:2 methylene chloride/methanol/triethylamine). The appropriate fractions were concentrated *in vacuo* to afford *syn*-3-aminohexahydro-4-hydroxy-1-phenyl-methlazepine (0.22 g, 58%%) as a colorless oil.

***syn*-Hexahydro-4-hydroxy-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine**

A solution of 4-benzyloxybenzoic acid (0.183 g, 0.8 mmol) in anhydrous tetrahydrofuran (2 ml) and N, N-dimethylformamide (0.5 ml) was treated with N,N'-carbonyldiimidazole ((0.15 g, 0.9 mmol) and stirred at room temperature for 1.5h. The solution was treated with *syn*-3-aminohexahydro-4-hydroxy-1-phenylmethylazepine (0.20 g, 0.9 mmol) in anhydrous tetrahydrofuran (1 ml). The mixture was stirred for eighteen hours, and then concentrated *in vacuo*. the residue was taken up in 1N sodium carbonate (20 ml), and

the aqueous mixture was extracted with toluene (2 X 25 ml) containing a small amount of 2-propanol. The combined organic extracts were dried (Na_2SO_4) and the concentrated residue was flash chromatographed on silica gel (eluted with 3:1 ethyl acetate/hexane) to afford *syn*-hexahydro-4-hydroxy-3-(4-penylmethoxy)-benzoylamino-1-phenylmethylazepine (0.17 g, 50%) as a viscous oil.

3,5-Bis(phenylmethoxy)-4-(2-phenylmethoxybenzoyl benzoic acid ester with *syn*-Hexahydro-4-hydroxy-3-(4-phenylmethoxy benzoyl-amino-1-phenylmethylazepine

A solution of 3,5-bis(phenylmethoxy)-4-(2-phenylmethoxybenzoyl)benzoic acid (0.245 g, 0.45 mmol) in anhydrous methylene chloride (1.5 ml) was treated with N,N-dimethylformamide (two drops), then with 2 N oxalyl chloride/methylene chloride (Aldrich, 0.30 ml, 0.60 mmol), and stirred for one hour under nitrogen. The solution was concentrated *in vacuo* and placed under high vacuum for one hour. *syn*-hexahydro-4-hydroxy-3-(4-phenylmethoxy)benzoyl-amino-1-phenylmethylazepine (0.170 g, 0.40 mmol) was dissolved in anhydrous methylene chloride (3 ml), treated with 4-dimethyl-aminopyridine (0.01 g) and triethylamine (0.12 ml, 1.2 mmol), and cooled in an ice bath under nitrogen. The acid chloride was removed from high vacuum and dissolved in anhydrous methylene chloride (2 ml), and was then added to the cooled solution. The mixture was allowed to warm to room temperature, stirred for one hour, and was partially concentrated *in vacuo*. The residual solution was deposited on a silica gel column and eluted (first with 2:1 hexane/methylene chloride, then with 1:1 hexane/methylene chloride) to afford (after concentration of the appropriate fractions) 3,5-bis(phenylmethoxy)-4-(2-phenylmethoxybenzoyl)- benzoic acid ester with *syn*-hexahydro-4-hydroxy-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.29 g 77%) as a white foam.

***syn*-(4-(3,5-Dihydroxy-4-(2-hydroxybenz yl)benzoyloxy))hexhydro-3-(4-hydroxybenzoylamino)az pine**

A cloudy suspension of 3,5-bis(phenylmethoxy)-4-(2-phenylmethoxybenzoyl-benzoic acid ester with *syn*-hexahydro-4-hydroxy-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.29 g, 0.30 mmol) in reagent ethanol (25 ml) was treated with $Pd(OH)_2/C$ (Aldrich, Pearlman's catalyst, 0.20 g, 20%) in a Parr bottle, then subjected to hydrogenation for twenty four hours at 50-52 psi. The hydrogen was evacuated and the solution was carefully filtered through Celite® under nitrogen, and the filter pad was washed with methanol (not to dryness). The filtrate was concentrated *in vacuo* to crude material, which was flash chromatographed on a short column of silica gel (eluted with 1:1 $CHCl_3$/EtOH) to afford a product (0.13 g) as a pale yellow foam. This was triturated from ether/ acetonitrile to afford *syn*-(4-(3,5-dihydroxy-4-(2-hydroxybenzoyl-benzoyl-oxy))hexahydro-3-(4-hydroxybenzoylamino) azepine (0.195 g, 62%) as a pale yellow powder (dihydrate): mp 177-179°C; R_f (1:1 $CHCl_3$/EtOH on silica) 0.45; IR (KBr) 1623 cm^{-1}, ^1H NMR (d_6-DMSO) δ 8.20 (d, 1H, J = 8Hz), 7.10 (s, 2H), 7.02 (d, 1H, J = 9 Hz), 6.91 (t, 1H, J -= 8Hz), 6.78 (d, 2H, J = 9Hz), 5.39 (br d, 1H, J = 7Hz), 4.48 (m, 1H), 3.00-3.20 (m, 4H), 2.05-2.20 (M, 1H), 1.70-2.00 (m, 3H). Anal. Calcd. for $C_{27}H_{26}N_2O8 \cdot 2H_2O$: C, 59.77; N, 5.57; H, 5.16. Found: C, 59.83; H, 5.39; N, 5.46.

anti-4-[3,5-Dihydroxy-4-(2-phenylcarbonyl-benzoyloxy-3-(4-hydroxybenzamido)azepine

To a solution of tran-4-(3,5-dibenzyloxy-4-phenyl carbonyl-benzoyloxy-3-(4-benzyloxybenzamido)-N-benzylazepine (40 mg, 0.042 mmol) was added Pd(OH)2 (Pearlman's catalyst) 20 mg, 50% on weight basis) and introduced H_2 gas at atmosphere pressure.

Trans-1-(4-hydroxybenzamido)-2-(4-benzyl-3,5-dihydroxybenzoyl xy) cycloheptane

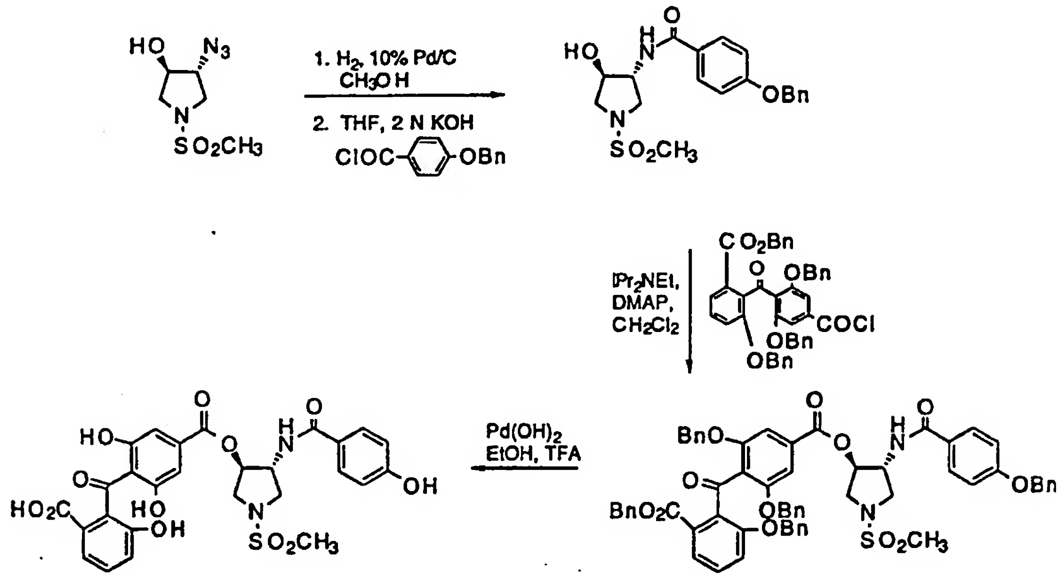
The catalyst $Pd(OH)_2$ on carbon (20%, moist, 20 mg) was added to a solution of trans-1-(4-benzoyloxybenzamido)-2-)4-

benzoyl-3,5-dibenzyloxybenzoyloxy)cycloheptane (215 mg, 0.28 mmol) in methanol (8.4 ml). The mixture was stirred vigorously at room temperature under 1 atm H_2 contained in a balloon for sixteen hours. The solid catalyst was removed by flash chromatography (SiO_2, 2:2:1/diethyl ether:hexane:methylene chloride) to give a white powder (112 mg, 84%): mp 224-226°C; ^1H NMR (CD_3OD) δ 7.52-7.56 (m, 2H), 7.02-722 (m, 5H), 6.94 (s, 2H), 6.71-6.75 (m, 2H), 5.10 (tm, J = 9.1 Hz, 1H), 4.35 (tm, J-9.3 Hz, 1H), 3.93 (s, 2H), 1.56-2.02 (m, 10H) IR (KBr) cm^{-1} 3389, 1687, 1626. Anal. calcd. for $C_{28}H_{29}O_6N$: C, 70.72; H, 6.15: N, 2.95. Found C, 70.39; H, 6.37; N, 2.67.

Trans-1-(4-hydroxybenzamido)-2-[4-(2-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy] cycloheptane

The catalyst $Pd(OH)_2$ on carbon (20%, moist, 9 mg) was added to a solution of trans-1-(4-benzyloxybenzamido)-2-[4-(2-benzyloxybenzoyl)-3,5-dibenzyloxybenzoyloxy] cycloheptane (112 mg, 0.13 mmol) in methanol (3.9 ml) and ethyl acetate (1.3 ml). The mixture was stirred vigorously at room temperature under 1 atm H_2 contained in a balloon for seventeen hours. The solid catalyst was removed by filtration through Florisil®. The filtrate was evaporated and purified by flash chromatography (SiO_2 2:2:1/ethyl acetate:hexane:methylene chloride) to give a pale yellow powder (40 mg, 61%): mp 234-236°C; ^1H NMR (CD_3OD) δ 7.56-7.59 (m, 2H), 7.47 (t, J-7.1 Hz, 1H), 7.23 (d, J=8.0 Hz, 1H), 7.00 (s, 2H), 6.96 (d, J=8.2 Hz, 1H), 6.74-6.78 (m, 2H), 5.15 (tm, J=9.3 Hz, 1H), 4.40 (tm, J=9.3 Hz, 1H), 1.58-2.05 (m, 10H) IR (KBr) cm^{-1} 3392, 1700, 1678, 1626. Anal. calcd. for $C_{28}H_{29}O_6N$: C, 66.53; H, 5.38; N, 2.77. Found: C, 66.37; H, 5.56; N, 2.47.

(±)-Trans-4-[4-(2-Carb xy-6-hydroxybenzoyl)-3,5- dihydroxy-b nz yloxy]-3-(4-hydroxybenzamido)-1-(m thylsulfonyl) pyrr lidine (COMPOUND 501)



501 600

(±)-Trans-4-Hydroxy-3-(4-benzyloxybenzamido)-1-(methylsulfonyl)-pyrrolidine

To 10% palladium on carbon (41 mg) wetted with methanol (1.0 ml) was added the azide (412 mg, 2.00 mmol) in methanol (9.0 ml). The flask was evacuated and filled with H_2 twice then allowed to stir under H_2 (1 atm) for 4 h. The mixture was filtered through Celite and washed through with methanol (100 ml). The methanol was evaporated, providing an off-white solid which was used without characterization.

To a 0°C solution of the above amino alcohol in THF (6.0 ml) was added 2 N KOH (1.0 ml). The ice bath was removed, and the acid chloride (approx. 0.75 eq) added portionwise over 2.5 h, until the starting material was gone as evidenced by thin layer chromatography. The mixture was diluted with CH_2Cl_2 (30 ml) and poured into H_2O (60 ml). Methanol (20 ml) was

added to disperse the emulsion, the layers were separated, and the aqueous layer extracted with CH_2Cl_2 (4 x 50 ml). The organic lyaers were combined, dried ($MgSO_4$) filtered and evaporated to provide the title compound as a white solid (593 mg, 76% over two steps). ^{1}H NMR (CD_3OD) δ 7.60 (d, J = 8.7 Hz, 2H), 7.25-7.10 (m, 5H), 6.85 (d, J = 9.0 Hz, 2H), 4.94 (s, 2H), 4.18-4.12 (m, 2H), 3.58-3.42 (m, 4H), 2.71 (s, 3H).

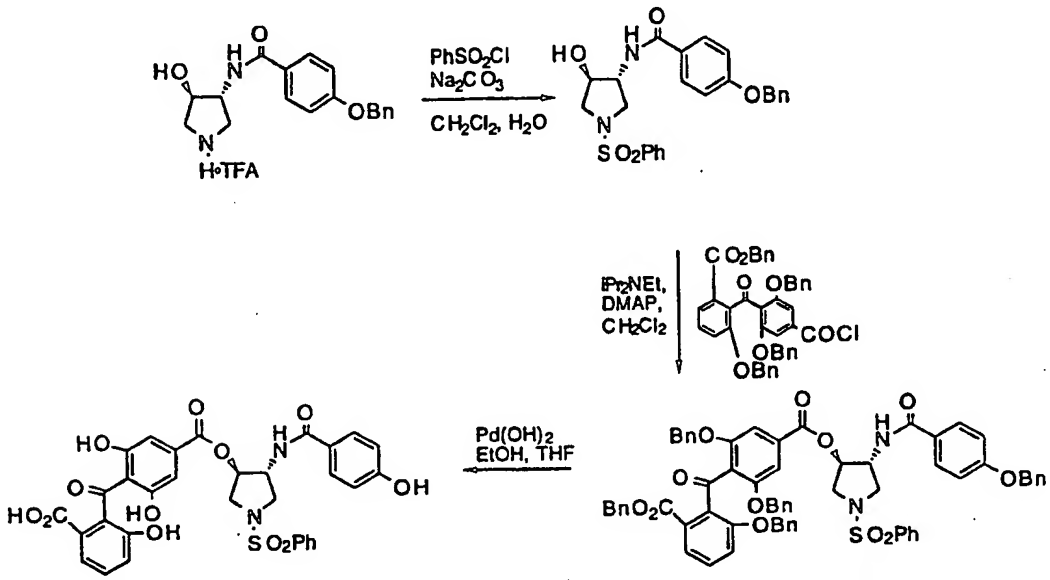
(±)-Trans-4-[4-(6-benzyloxy-2-(benzyloxycarbonyl)benzoyl]-3,5-dibenzyloxybenzoyloxy)-3-(4-benzyloxybenzamido)-1-(methyl sulfonyl)-pyrrolidine (COMPOUND 600)

To a 0°C solution of the product of the previous step (202 mg, 0.518 mmol), diisopropylethylamine (98 μl, 1.2 eq., 0.565 mmol) and 4-dimethylaminopyridine (58 mg, 1.0 eq., 0.471 mmol) in CH_2Cl_2 (8.0 ml) under N_2 was added a solution of the acid chloride (0.471 mmol) in CH_2Cl_2 (4.0 ml). The reaction was allowed to warm to room temperature with stirring over 16 h. The cloudy reaction mixture was diluted with CH_2Cl_2 (50 ml) and washed with satd. $NaHCO_3$ (30 ml) then brine (30 ml). The aqueous layers were extracted with CH_2Cl_2 (50 ml) each. The organics were combined, dried ($MgSO_4$), filtered and evaporated to a light yellow oil. Flash column chromatography (1:1 hexane:ethyl acetate) provided the title product as an off white foam (371 mg, 75%): mp 73-79°C; IR (KBr) 3367, 1723, 1660, 1230, 1112, 745, 697 cm-1; 1H NMR ($CDCl_3$) δ 7.80 (d, J = 8.7 Hz, 2H), 7.40-7.10 (m, 20 H), 7.10-7.00 (m, 8H), 6.98 (s, 2H), 6.97 (d, J = 8.3 Hz, 2H), 5.48 (m, 1H), 5.15 (s, 2H), 5.09 (s, 2H), 4.79 (s, 4H), 4.74 (m, 1H), 4.72 (s, 2 H), 3.99 (dd, J = 12.3, 5.5 Hz, 1H), 3.78 (dd, J = 11.0, 6.0 Hz, 1H), 3.58 (dd, J = 11.0, 3.3 Hz, 1H), 3.51 (dd, J = 12.3, 2.1 Hz, 1H) 2.78 (s, 3H); LRMS (M^+ + H) 1051 (65), 797 (21), 661 (100), 571 (38); HRMS calcd for $C_{62}H_{55}N_2O_{12}S$ (M^+ + H) 1051.3476, found 1051.3433; Anal. Calcd. for $C_{62}H_{54}N_2O_{12}S \cdot H_2O$: C, 69.65; H, 5.28; N 2.62; S, 3.00; found C, 69.79; H, 5.30; N, 2.59; S, 2.82.

(±)-Trans-4-[4-(2-Carboxy-6-hydr xybenz yl)-3,5-dihydroxy benz yloxy]-3-(4-hydroxybenzamido)-1-(m thylsulfonyl) pyrr lidine (COMPOUND 501)

To Compound 600 (323 mg, 0.307 mmol) and $Pd(OH)_2$ (50 mg of a 20% by weight powder) under N_2 were added ethanol (28 ml) then trifluoroacetic acid (28 μl). The flask was evacuated and filled with H_2 three times, then stirred under H_2 27 h. The mixture was filtered through Celite, washed with methanol (40 ml) and the filtrate evaporated to a yellow glass. A DMF solution of the reaction product was purified by reverse phase HPLC (21 x 250 mm C_{18} column) to provide Compound 501 (137 mg, 74%) as a yellow powder after lyophilization: mp 167-170, 179-187°C (dec); IR (KBr) 3394, 1708, 1607, 1235, 762 cm^{-1}; ^1H NMR (CD_3OD) δ 7.53 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 7.6 Hz, 1H), 7.07 (dd, J = 7.9, 8.1 Hz, 1 H), 6.82 (d, J = 8.2 Hz, 1H), 6.73 (s, 2H), 6.62 (d, J = 8.7 Hz, 2H), 5.29 (dt, J = 5.5, 3.1 Hz, 1H), 4.48 (dt, J = 6.2, 4.2 Hz, 1H), 3.73 (dd, J = 12.0, 5.5 Hz, 1H), 3.67 (dd, J = 10.7, 6.9 Hz, 1H), 3.35 (dd, J = 12.0, 2.8 Hz, 1H), 3.28 (dd, J = 10.6, 4.4 Hz, 1H), 2.75 (s, 3H); LRMS (M^+ + H) 601 (100), 301 (54), 283 (56); HRMS calcd for $C_{27}H_{25}N_2O_{12}S$ (M^+ + H) 601.1128, found 601.1831; Anal. Calcd. for $C_{27}H_{24}N_2O_{12}S \cdot 2.5\ H2O$: C, 50.23; H, 4.53; N, 4.34; S, 4.97; found C, 50.22; H, 4.36; N, 4.37; S, 4.77.

(±)-Trans-4-[4-(2-Hydroxycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)-1-(phenylsulfonyl) pyrrolidine (COMPOUND 502)



(±)-Trans-3-(4-benzyloxybenzamido)-4-hydroxy-1-(phenylsulfonyl)-pyrrolidine

To a slurry of starting hydroxyamide (150 mg, 0.352 mmol) in H_2O (8.8 ml) and CH_2Cl_2 (8.8 ml) were added anhydrous Na_2CO_3 (112 mg, 3.0 eq, 1.06 mmol) then benzenesulfonyl chloride (58 µl, 0.458 mmol, 1.3 eq), and the mixture stirred at room temperature 15 h. The solution was then diluted with CH_2Cl_2 (20 ml) and poured into H_2O (20 ml) and methanol (4 ml). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 30 ml). The organics were combined, dried ($MgSO_4$), filtered and evaporated to a white powder (159 mg, quant yield): ^1H NMR (CD_3OD) δ 7.62 (d, J = 7.7 Hz, 2H), 7.43 (d, J = 8.9 Hz, 2H), 7.35-7.30 (m, 3H), 7.25-7.10 (m, 5H), 6.80 (d, J = 8.8 Hz, 2H), 4.95 (s, 2H), 4.06-4.00 (m, 1H), 3.95-3.90 (m,

1H), 3.50-3.35 (m, 2H), 3.15 (dd, J = 10.6, 3.9 Hz, 1H), 2.99 (dd, J = 10.8, 3.2 Hz, 1H).

(±)-Trans-4-[4-(6-benzyloxy-2-(benzyloxycarbonyl)benzoyl]-3,5-dibenzyloxybenzoyloxy)-3-(4-benzyloxybenzamido)-1- (phenyl sulfonyl)-pyrrolidine (COMPOUND 601)

To a solution of the prior product (159 mg, 0.352 mmol) in CH_2Cl_2 (6.0 ml) were added 4-dimethylaminopyridine (43 mg, 0.352mmol, 1.0 eq), diisopropylethylamine (74 μl, 0.42 mmol, 1.2 eq) then a solution of acid chloride (0.383 mmol, 1.1 eq) in CH_2Cl_2 (3.0 ml). The mixture was stirred at room temperature under N_2 14 h. The reaction mixture was then diluted with CH_2Cl_2 (30 ml), and washed with 10% $NaHCO_3$ (50 ml) then brine (50 ml). The aqueous layers were combined and extracted with CH_2Cl_2 (2 x 50 ml). The organics were combined, dried ($MgSO_4$), filtered and evaporated. Flash column chromatoghraphy of the residue (2:1 hexane:ethyl acetate) on silica gel provided the title compound (183 mg, 47%): ^{1}H NMR ($CDCl_3$) δ 7.77 (d, J = 6.7 Hz, 2H), 7.70 (d, J = 8.8 Hz, 2H), 7.47-7.16 (m, 14H), 7.15-7.05 (m, 6H), 7.04-6.94 (m, 3H), 6.90-6.83 (m, 3H), 6.42 (d, J = 6.7 Hz, 1H), 5.30 (dt, J = 5.1, 2.6 Hz, 1H), 5.18 (s, 2H), 5.13 (s, 2H), 4.78 (m, 2H), 4.76 (s, 2H), 4.72 (s, 2H), 4.64-4.60 (m, 1H), 3.88 (dd, J = 12.6, 5.4 Hz, 1H), 3.74-3.65 (m, 1H), 3.60-3.38 (m, 2H).

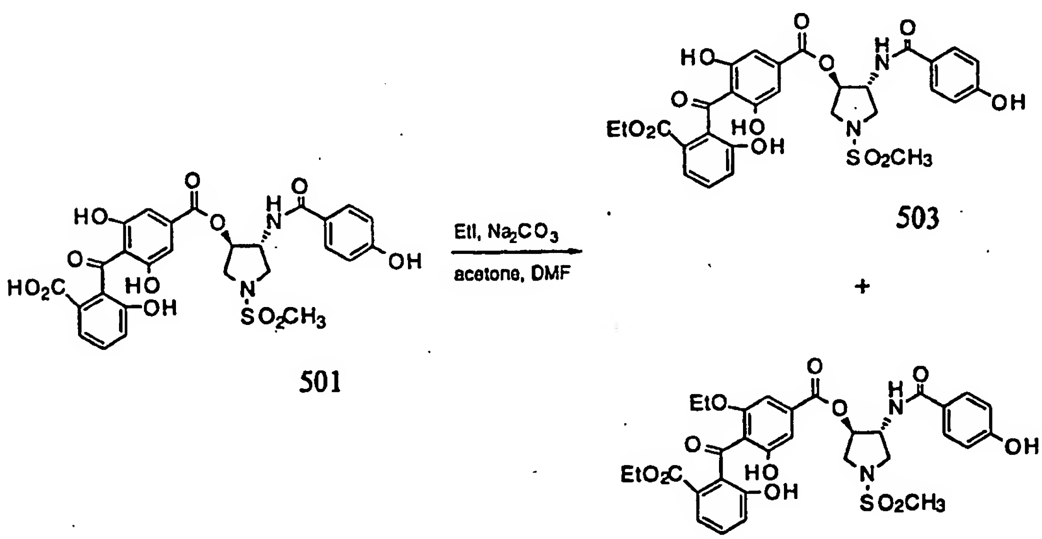
(±)-Trans-4-[4-(2-Hydroxycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)-1-(phenylsulfonyl) pyrrolidine (COMPOUND 502)

To a solution of Compound 601 (183 mg, 0.164 mmol) in THF (7.4 ml) and ethanol (7.4 ml) was added $Pd(OH)_2$ (92 mg, of a 20% by weight powder). The flask was evacuated and filled with H_2 twice, then stirred under H_2 (1 atm) for 20 h. The suspension was filtered through Celite, washed through with methanol (50 ml), and evaporated to a yellow oil. Purification by HPLC (21 x 250 mm C_{18} column) provided Compound 502 (75 mg, 69%) as a fluffy yellow powder after lyophilization: mp 185-208°C; IR (KBr) 3402, 1709, 1636, 1608, 1232 cm-1; 1H NMR

(CD_3OD) δ 7.53 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 7.3 Hz, 1H), 7.22-7.11 (m, 3H), 7.09 (dd, J = 8.1, 7.9 Hz, 1H), 6.84 (d, J = 7.2 Hz, 1H), 6.61 (d, J = 8.7 Hz, 2H), 6.35 (s, 2H), 4.99 (app t, J = 2.2 Hz, 1H), 4.92 (dd, J = 5.6, 2.8 Hz, 1H), 3.62 (dd, J = 13.0, 4.3 Hz, 1H), 3.50 (dd, J = 10.8, 6.0 Hz, 1H), 3.39 (dd, J = 10.7, 2.4 Hz, 1H), 3.32 (bd, J = 13.1 Hz, 1H); HRMS (M^+ + H) calcd 663.1285, found 663.1302; Anal. Calcd. for $C_{32}H_{26}N_2O_{12}S \cdot 1\ H_2O$: C, 56.47; H, 4.15; N, 4.12; S, 4.71; found: C, 56.56; H, 4.17; N, 4.09; S, 4.58.

(±)-Trans-4-[4-(2-Ethoxycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydr xyb nzamido)-1-(methylsulf nyl) pyrr lidine (COMPOUND 503)

(±)-Trans-4-[4-(2-Ethoxycarbonyl-6-hydroxybenzoyl)-3-ethoxy-5-hydroxybenzoyloxy]-3-(4-hydroxybenzamido)-1-(methylsulfonyl) pyrrolidine (COMPOUND 504)



501 503 504

To a solution of Compound 501 (70 mg, 0.12 mmol) in acetone (5.6 ml) under N_2 were added Na_2CO_3 (anhyd, 25 mg, 0.23 mmol, 2.0 eq) then iodoethane (47 µl, 0.58 mmol, 5.0 eq). After stirring at room temperature 3h, a solid began to form. After 5h, more iodoethane (0.47 ml, 50 eq) was added. After 22h, more iodoethane (0.47 ml, 50 eq) was added, and after another 24 h DMF (1.0 ml) was added to force the precipitate to dissolve. The clear yellow solution was stirred 20 h more, evaporated to approx. 2 ml, then partitioned between H_2O (30 ml) and CH_2Cl_2 (30 ml). The layers were separated, and the aqueous layer extracted with CH_2Cl_2 (5 x 20 ml). The organics were combined, dried ($MgSO_4$), filtered and evaporated. The yellow residue was purified by reverse phase HPLC (21 x 250 mm C_{18} column) to provide Compound 503 (27 mg, 37%) as a yellow

power after lyophilization, as well as Compound 504 (11 mg, 14%) as a light yellow powder after lyophilization.

Data for Compound 503 are mp 146-162°C; IR (KBr) 3404, 3364, 2361, 1714, 1637, 1576, 1300, 1231 cm^{-1}; ^1H NMR (CD3OD) δ 8.33 (d, J = 6.6 Hz, 1H), 7.53 (d, J = 8.7 Hz, 2H), 7.27 (d, J = 7.7 Hz, 1H), 7.08 (dd, J = 8.1, 7.8 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.74 (s, 2H), 6.62 (d, J = 8.7 Hz, 2H), 5.29 (dd, J = 5.9, 3.2 Hz, 1H), 4.53-4.47 (m, 1H), 3.93 (q, J = 7.1 Hz, 2H), 3.73 (dd, J = 12.1, 5.6 Hz, 1H), 3.68 (dd, J = 10.3, 6.5 Hz, 1H), 3.35 (dd, J = 12.0, 2.9 Hz, 1H), 3.28 (dd, J = 10.7, 4.5 Hz, 1H), 2.76 (s, 3H), 0.92 (t, J = 7.1 Hz, 3H); LRMS (M^+ + H) 629 (100), 555 (10), 203 (41); HRMS (M^+ + H) calcd 629.1441, found 629.1476; Anal. Calcd. for $C_{29}H_{28}N_2O_{12}S \cdot 1.25\ H_2O$: C, 53.49; H, 4.72; N, 4.30; S, 4.92; found: C, 53.66; H, 4.61; N, 4.29; S, 4.87.

Data for Compound 504 are mp 129-134, 140-148°C (dec); IR (KBr) 3404, 2362, 1715, 1633, 1573, 1300, 1229 cm^{-1}; ^1H NMR (CD_3OD) δ 7.53 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 7.7 Hz, 1H), 7.12 (dd, J = 8.1, 7.9 Hz, 1H), 7.00 (d, J = 1.5 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 6.76 (d, J = 1.5 Hz, 1H), 6.63 (d, J = 8.8 Hz, 2H), 5.30 (dd, J = 5.4, 3.1 Hz, 1H), 4.57-4.50 (m, 1H), 3.92 (q, J = 7.1 Hz, 2H), 3.76-3.68 (m, 2H), 3.56 (q, J = 6.9 Hz, 2H), 3.39 (dd, J = 11.9, 3.1 Hz, 1H), 3.28 (dd, J = 10.7, 4.6 Hz, 1H), 2.78 (s, 3H), 0.91 (t, J = 7.1 Hz, 3H), 0.50 (t, J = 6.9 Hz, 3H); HRMS (M^+ + H) calcd 657.1754, found 657.1619; Anal. Calcd. for $C_{31}H_{32}N_2O_{12}S \cdot H_2O$: C, 55.19; H, 5.08; N, 4.15; S, 4.75; found: C, 55.18; H, 4.92; N, 4.10; S, 4.66.

syn-(4-(3,5-Dihydroxy-4-(2-hydroxybenzoyl)benzoyloxy)hexahydro-3-(4-hydroxybenzoylamino)azepine (COMPOUND 505)

3-Acetylaminohexahydro-1-phenylmethylazepin-2,4-dione

A solution of hexahydro-1-phenylazepin-2,3,4-trione-3-oxime (1.23 g, 5 mmol) in 4:1 acetic acid/acetic anhydride (20 ml) was treated with Raney nickel (Aldrich, one-half tsp) in a Parr bottle and subjected to hydrogenation over 18 h at 40-45 psi and room temperature. The mixture was carefully evacuated of hydrogen and filtered through Celite. The filter pad was then washed with methanol (with care taken not to let the filter pad become dry). The filtrate was concentrated *in vacuo* and the residue diluted with toluene and further concentrated to remove most of the acetic acid. The residue was chilled on an ice bath and treated with saturated sodium bicarbonate carefully to avoid excessive bubbling. The cloudy aqueous solution was extracted with methylene chloride (3x50 ml, and the combined organic solution dried (Na_2SO_4) and concentrated *in vacuo*. The residue was flash chromatographed on silica gel (eluted with 19:1 methylene chloride/methanol) to afford 3-acetylaminohexahydro-1-phenylmethylazepin-2,4-dione (1.11 g, 81%) as a white solid.

syn-3-Aminohexahydro-4-hydroxy-1-phenylmethylazepin-2-one

A solution of 3-acetylaminohexahydro-1-phenylmethylazepin-2,4-dione (0.82 g, 3.0 mmol) in absolute ethanol (15 ml) was treated with sodium borohydride (0.23 g, 6 mmol) and stirred for 30 min, then treated with water (5 ml) and concentrated *in vacuo*. The aqueous residue was extracted with methylene chloride (3x25 ml) and the combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo*, and taken up in 2:1 ethanol/water (7.5 ml). Concentrated hydrochloric acid (2.5 ml) was added, and the mixture was refluxed for 2h and partially concentrated, then diluted with water (25 ml). The aqueous acidic mixture was extracted with ether (25 ml), and the aqueous solution basified with 30% sodium hydroxide and extracted with methylene chloride (3x40 ml). The combined

methylene chloride extracts were washed with water (25ml), dried (Na_2SO_4), and concentrated *in vacuo* to a yellow solid, which was recrystallized from ethyl acetate to afford *syn*-3-aminohexahydro-4-hydroxy-1-phenylmethylazepin-2-one (0.42 g, 60%) as a white solid.

syn-3-Aminohexahydro-4-hydroxy-1-phenylmethylazepine

A cooled (5°C) solution of lithium aluminum hydride/tetrahydrofuran (Aldrich, 1.0 N, 5.1 ml) under nitrogen was treated with *syn*-3-aminohexahydro-4-hydroxy-1-phenylmethylazepin-2-one (0.40 g, 1.7 mmol) in portions so that the pot temperature did not exceed 15°C. The mixture was refluxed for 6.5h, cooled on an ice bath, and carefully treated with water (0.21 ml), 15% sodium hydroxide (0.21 ml), and water (0.63 ml). The suspension was allowed to stir for 5 days, during which time the product partially decomposed (optimal time is 2 - 5 hours). The suspension was filtered, and the filtrate was concentrated *in vacuo* and chromotographed on silica gel (eluted with 90:8:2 methylene chloride/methanol/triethylamine). The appropriate fractions were concentrated *in vacuo* to afford *syn*-3-aminohexahydro-4-hydroxy-1-phenylmethylazepine (0.22 g, 58%) as a colorless oil.

syn-Hexahydro-4-hydroxy-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine

A solution of 4-benzyloxybenzoic acid (0.183 g, 0.8 mmol) in anhydrous tetrahydrofuran (2 ml) and N,N-dimethylformamide (0.5 ml) was treated with N,N^1-carbonyldiimidazole (0.15 g, 0.9 mmol) and stirred at room temperature for 1.5h. The solution was treated with *syn*-3-aminohexahydro-4-hydroxy-1-phenylmethylazepine (0.20 g, 0.9 mmol) in anhydrous tetrahydrofuran (1 ml), and the mixture was stirred for 18 h, then concentrated *in vacuo*. The residue was taken up in 1N sodium carbonate (20 ml), and the aqueous mixture was extracted with toluene (2x25 ml) containing a little 2-propanol. The combined organic extracts were dried (Na_2SO_4) and the concentrated residue was flash chromatographed

on silica gel (eluted with 3:1 ethyl acetate/hexane) to afford *syn*-hexahydro-4-hydroxy-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.17 g, 50%) as a viscous oil.

3,5-Bis(phenylmethoxy)-4-(2-phenylmethoxybenzoyl)benzoic acid ester with *syn*-Hexahydro-4-hydroxy-3-(4-phenylmethoxy)benzoyl amino-1-phenylmethylazepine

A solution of 3,5-bis(phenylmethoxy)-4-(2-phenylmethoxybenzoyl)benzoic acid (0.245 g, 0.45 mmol) in anhydrous methylene chloride (1.5 ml) was treated with N,N-dimethylformamide (2 drops), then with 2.0 N oxalyl chloride/methylene chloride (Aldrich, 0.30 ml, 0.60 mmol), and stirred for one hour under nitrogen. The solution was concentrated *in vacuo* and placed under high vacuum for one hour. *syn*-Hexahydro-4-hydroxy-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.170 g, 0.40 mmol) was dissolved in anhydrous methylene chloride (3 ml), treated with 4-dimethylaminopyridine (0.001 g) and triethylamine (0.12 ml, 1.2 mmol), and cooled on an ice bath under nitrogen. The acid chloride was removed from high vacuum and dissolved in anhydrous methylene chloride (2 ml), then added to the cooled solution, and the mixture was allowed to warm to room temperature, stirred for one hour, and partially concentrated *in vacuo*. The residual solution was deposited on a silica gel column and eluted (first with 2:1 hexane/methylene chloride, then with 1:1 hexane/methylene chloride) to afford (after concentration of the appropriate fractions) 3,5-bis(phenylmethoxy)-4-(2-phenylmethoxybenzoyl)benzoic acid ester with *syn*-hexahydro-4-hydroxy-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.29 g, 77%) as a white foam.

syn-(4-(3,5-Dihydroxy-4-(2-hydroxybenzoyl)benzoyloxy))hexahydro-3-(4-hydroxybenzoylamino)azepine (COMPOUND 505)

A cloudy suspension of 3,5-bis(phenylmethoxy)-4-(2-phenylmethoxybenzoyl)benzoic acid ester with *syn*-hexahydro-4-hydroxy-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.29 g, 0.30 mmol) in reagent ethanol (25 ml) was treated with

20% $Pd(OH)_2/C$ (Aldrich, Pearlman's catalyst, 0.20 g) in a Parr bottle, then subjected to hydrogenation for 24h at 50 - 52 psi. The hydrogen was evacuated and the solution was carefully filtered through Celite under nitrogen, and the filter pad was washed with methanol (not to dryness). The filtrate was concentrated *in vacuo* to crude material, which was flash chromatographed on a short column of silica gel (eluted with 1:1 $CHCl_3$/EtOH) to afford 0.13 g of product as a pale yellow foam. This was triturated from ether/acetonitrile to afford *syn*-(4-(3,5-dihydroxy-4-(2-hydroxybenzoyl)benzoyloxy)) hexahydro-3-(4-hydroxybenzoylamino)azepine (0.95 g, 62%) as a pale yellow powder (dihydrate); mp 177-179°C. R_f (1:1 $CHCl_3$/EtOH on silica) 0.45; IR (KBr): 1623 cm^{-1}; ^1H NMR (d_6-DMSO) δ 8.20 (d, 1H, J = 8 Hz), 7.65 (d, 2H, J = 9 Hz), 7.57 (dt, 1H, J = 8, 1.5 Hz), 7.29 (dd, 1H, J = 8, 1.5 Hz), 7.10 (s, 2H), 7.02 (d, 1H, J = 8 Hz), 6.91 (t, 1H, J = 8 Hz), 6.78 (d, 2H, J = 9 Hz), 5.39 (br d, 1H, J = 7 Hz), 4.48 (m, 1H), 3.00 - 3.20 (m, 4H), 2.05 - 2.20 (m, 1H), 1.70 - 2.00 (m, 3H). Anal. Calcd. for $C_{27}H_{26}N_2O_8 \cdot 2H_2O$: C, 59.77; H, 5.57; N, 5.16. Found: C, 59.83; H, 5.39; N, 5.46.

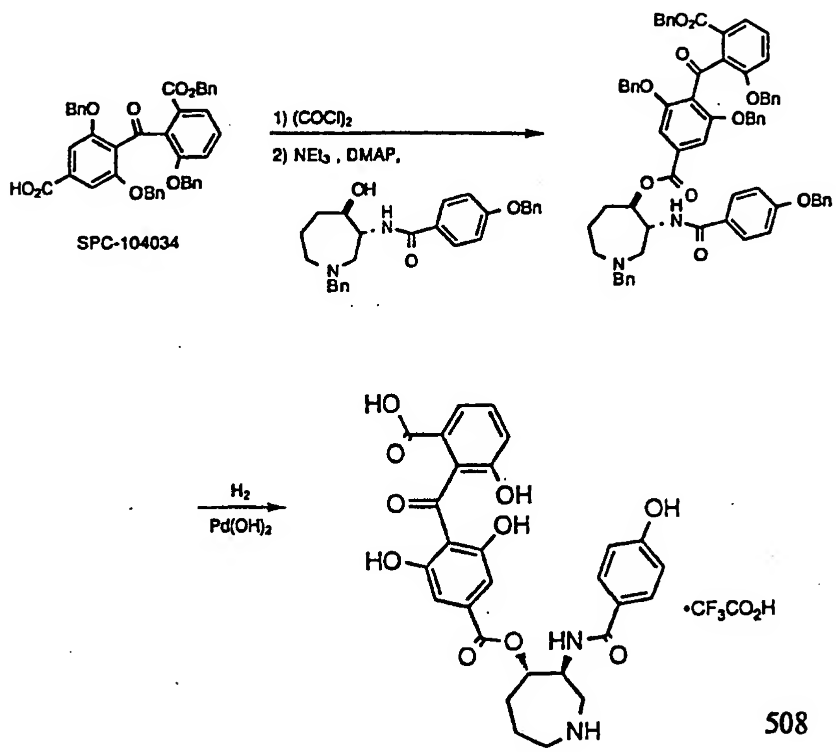
Anti-4-[3,5-Dihydroxy-4-(2-hydr xyphenylcarbonyl)]benzoyl xy-3-(4-hydroxyb nzamido)az pine (COMPOUND 506)

To a solution of anti-3-(4-benzyloxybenzamido)-4-[3,5-dibenzyloxy-4-(2-benzyloxyphenylcarbonyl)]benzoyloxy-N-benzylazepine (150 mg, 0.156 mmol) in EtOAc/EtOH (6 ml, 1:1) was added $Pd(OH)_2$ (Pearlman's catalyst) (90 mg, 60% on weight basis), and then H_2 at atmospheric pressure. After stirring vigorously for 24h at room temperature, the reaction mixture was filtered through a pad of celite. The filtrate was concentrated and purified on flash column (silica gel: 50 ml; eluted with 20% ethanol in methylene chloride). Compound 506 was obtained as yellow powder (30 mg, 38%): mp 174 - 176°C; ^1H NMR (DMSO) δ 7.65 (d, J = 8.64, 2H, ArH), 7.54 (td, 1H, ArH), 7.26 (dd, J = 1.6, 7.9 Hz, 1H, ArH), 6.70 (d, J = 6.48, 1H, ArH), 6.98 (s, 2H, ArH), 6.87 (td, 1H, ArH), 6.77 (d, J = 8.67 Hz, 2H, ArH), 5.18 (m, 1H, 4CH), 4.19 (m, 1H, 3 CH), 2.94 - 2.88 (dd, 1H, CH_2N), 2.83 - 2.73 (m, 3H, CH_2N), 1.91 (m, 2H, 6 CH_2), 1.74 and 1.64 (m and m, 2H, 5 CH_2); IR (KBr) cm^{-1} 3394, 1704, 1623, 1609, and 1504. Anal. calcd. for $C_{27}H_{26}N_2O_8 \cdot 1\ 1/4\ H_2O$: C, 61.30; H, 5.43; N, 5.29. Found: C, 61.33; H, 5.29; N, 4.96.

Trans-1-(4-benzyloxybenzamido)-2-[4-(2-benzyloxycarbonylbenzoyl)-3,5-dibenzyloxybenzoyloxyl)cycloheptane (COMPOUND 507)

An oven-dried 25ml 3-neck round bottom flask, under N_2, was charged with trans-2-(4-benzyloxybenzamido) cycloheptanol (204 mg, 0.6 mmol), 4-(2-benzyloxycarbonyl benzoyl)-3,5-dibenzyloxybenzoic acid (376 mg, 0.66 mmol), 1,3-dicyclohexylcarbodiimide (136 mg, 0.66 mmol), 4-dimethyl-aminopyridine (74 mg, 0.66 mmol), and dry methylene chloride (4.5 ml). The resultant suspension was stirred at room temperature for 17 hours, diluted with methylene chloride (6ml), washed with water (5 ml x 3), and dried $MgSO_4$. The solvent was evaporated and the residue was chromatographed (SiO_2, 1:1:2/ diethyl ether:methylene chloride:hexane) to give a white powder (429 mg, 80%): mp 153-154°C; ^1H NMR ($CDCl_3$) δ 6.89 - 7.68 (m, 30H), 6.33 (d, J = 8.6 Hz, 1H), 5.16 (s, 2H), 5.13 (tm, J = 9.4 Hz, 1H), 5.04 (s, 2H), 4.95 (ABq, J = 14.2, 12.2 Hz, 4H), 4.45 (tm, J = 9.3 Hz, 1H), 1.55 - 2.08 (m, 10H) IR KBr 3466, 3367, 1735, 1717, 1679 cm^{-1}. Anal. calcd for $C_{57}H_{51}O_9N$: C, 76.58; H, 5.75; N, 1.57. Found: C, 76.61; H, 5.82; N, 1.35.

Trans-4-(4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxy benzoyloxy)-3-(4-hydroxybenzamid)azepine Trifluoroacetic Acid Salt (COMPOUND 508) Trifluoroacetic Acid Salt of Balanol



508

Trans-N-Benzyl-4-(4-(6-benzyloxy-2-(benzyloxycarbonyl)benzoyl)-3,5-dibenzyloxybenzoyloxy)-3-(4-benzyloxybenzamido)azepine (COMPOUND 602)

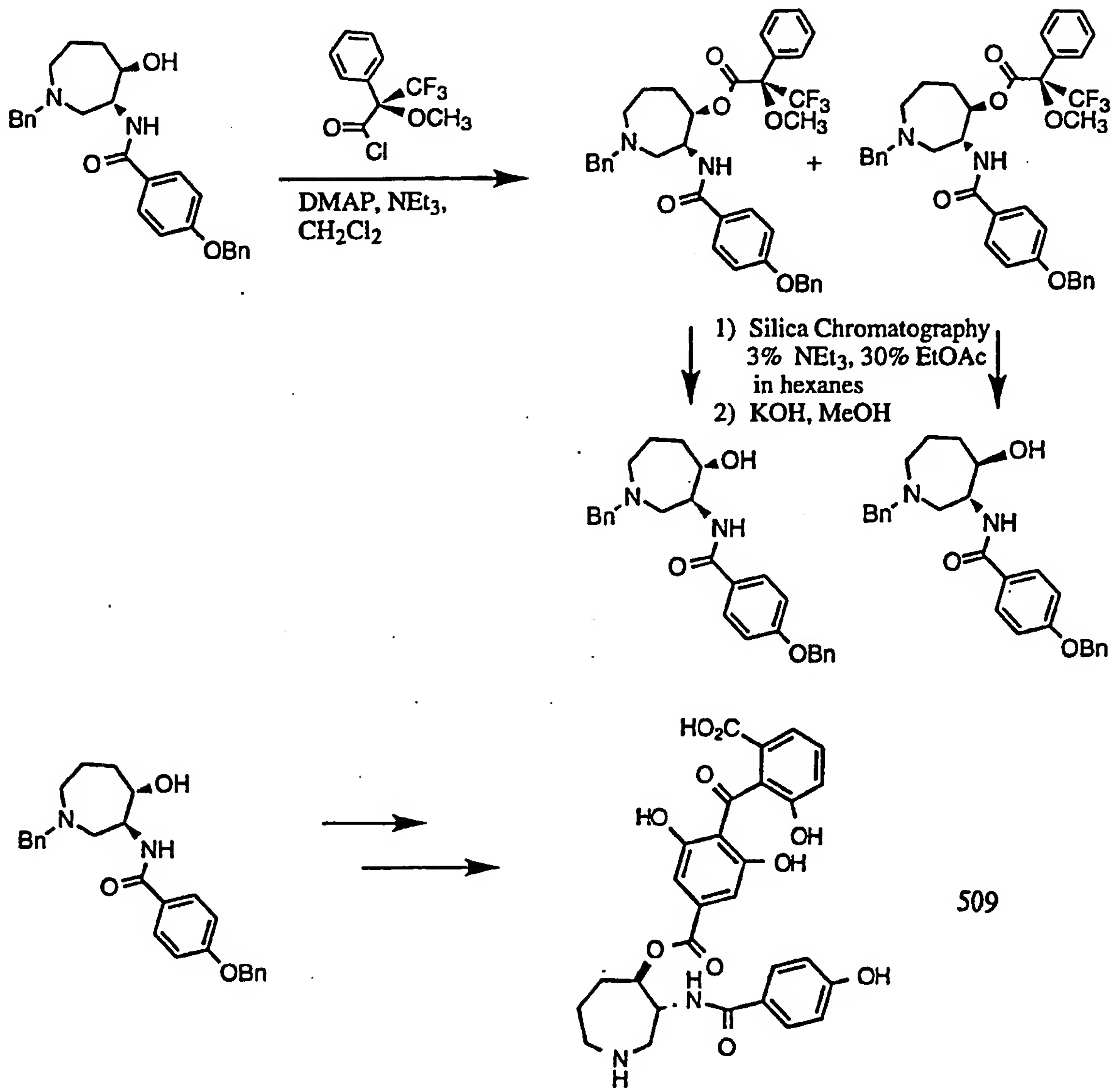
A solution of 84 mg (0.12 mmol) of 4-(6-benzyloxy-2-(benzyloxycarbonyl)benzoyl)-3,5-dibenzyloxybenzoic acid in 2 ml of methylene chloride containing a trace (approximately 0.5 μL) of dimethylformamide was cooled to 0°C. Oxalyl chloride (11.9 μL, 0.136 mmol) was added, and the mixture was stirred under a nitrogen atmosphere for 1.5 h. An additional 11.9 μL of oxalyl chloride was added, and the mixture was stirred for an additional 1.5 h. The reaction mixture was evaporated, and the residue was evaporated twice from 15 ml of methylene chloride. The residue was dissolved in 2 ml of methylene chloride, and was added to a solution of 59.1 mg (0.137 mmol) of trans-N-benzyl-3-(4-benzyloxybenzamido)-4-hydroxyazepine, 19.0 μl (0.136 mmol) of triethylamine, and 3 mg of DMAP in 1.5

ml of methylene chloride at 0°C. The mixture was stirred at room temperature under a nitrogen atmosphere for 22 h, after which it was diluted with 30 ml of methylene chloride, washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated to give 139 mg of the crude product. Chromatography on silica gel eluting with 6/4 hexane - ethyl acetate gave 89.4 mg (66%) of Compound 602 as a yellow oil, which was used directly in the next step.

Trans-4-(4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihyroxybenzoyloxy)-3-(4-hydroxybenzamido)azepine Trifluoroacetic Acid Salt (COMPOUND 508)

A solution of 65 mg (0.060 mmol) of Trans-N-benzyl-4-(4-(6-benzyloxy-2-(benzyloxycarbonyl)benzoyl)-3,5-dibenzyloxybenzoyloxy)-3-(4-benzyloxybenzamido)azepine in 30 ml of 1/2/2 methanol/ethanol/methylene chloride was treated with 17 μl of trifluoroacetic acid and evaporated. The residue was dissolved in 12 ml of 3/1 ethanol/methanol, 15.6 mg of moist 10% palladium hydroxide on carbon was added, and the mixture was shaken on a Parr apparatus under 50 psi of hydrogen for 5 h. The mixture was filtered, evaporated, and the residue was chromatographed on a 21 x 250 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0-100% B over 60 min, flow: 15 ml/min). The pure fraction was evaporated and then lyophilized from water to give 11.2 mg (33%) of the title compound as a yellow fluffy solid. IR (KBr) : 1701, 1674, 1636, 1608, 1425, 1234, 1200 cm-1; FABMS: *m/z* 573 (M + Na), 551 (M+H); HRMS: calcd for $C_{28}H_{27}N_2O_{10}$: 551.1665, found 551.1697.

ent-Balanol (COMPOUND 509)



(S)-Mosher's acid chloride

Note that the chirality label is changed going from acid to acid chloride. (R)- (+)-α-Methoxy-α-trifluoromethyl acetic acid (5.1 g, 21.8 mmol) was slurried in hexane (3 ml). DMF (2 drops) was added followed by a 2M methylene chloride solution of oxalyl chloride (33 ml, 66 mmol). The solution was refluxed for 3 h, cooled to rt, concentrated and distilled by

kugelrohr (T = 45°C at 0.1 mm Hg) to give the product as a clear oil.

Trans-N-Benzyl-3-(4-benzyloxybenzamido)-4-((R)-2-methoxy-2-trifluoromethylacetoxy)hexamethyleneimine

Trans-N-Benzyl-3-(4-benzyloxybenzamido)-4-hydroxy-hexamethyleneimine (1.2 g, 2.79 mmol), DMAP (4 mg, 0.3 mmol) and triethylamine (2.25 g, 3.1 ml, 22.3 mmol) were dissolved in methylene chloride (10 ml) and treated with (S)-Mosher's acid chloride (1.8 g, 1.3 ml, 7 mmol). When TLC indicated complete reaction, the mixture was concentrated and flashed (7 x 15 cm, 3% triethylamine in 4/1 : ethyl acetate/hexanes). The products were separated into clean upper, mixed and clean lower fractions. All three fractions were each again chromatographed on a Dynamax®-60 silica column (41.4 mm ID X 30 cm length) using a linear gradient from 20% to 60% B (A = hexanes, B = 10% triethyl amine in ethyl acetate) over 60 m at 25 ml/min. The clean upper HPLC fractions from the upper and mixed runs were combined (490 mg) for hydrolysis ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.6-1.8 (2H, m), 1.94 (2H, m), 2.48 (1H, m), 2.77 (1H, m), 2.9-3.0 (2H, m), 3.50 (1H, d, J = 13 Hz), 3.54 (3H, s), 3.72 (1H, d, J = 13 Hz), 4.1-4.2 (1H, m), 5.14 (2H, s), 5.28 (1H, m), 6.84-7.65 (14H, m).

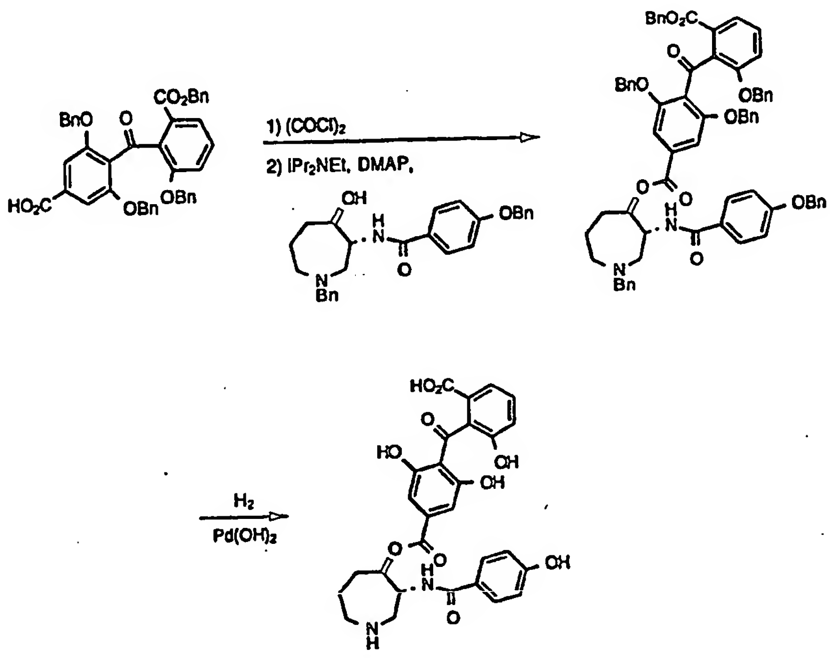
The clean lower HPLC fractions from the lower run were combined (260 mg) for hydrolysis. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.64-1.8 (2H, m), 1.8-1.94 (2H, m), 2.53 (1H, m), 2.77 (1H, m), 2.9-3.0 (2H, m), 3.50 (1H, d, J = 13 Hz), 3.52 (3H, s), 3.72 (1H, d, J = 13 Hz), 4.1 (1H, m), 5.13 (2H, s), 5.28 (1H, m), 6.84-7.54 (14H, m).

The upper ester fraction (490 mg, 0.76 mmol) was dissolved in methanol (5 ml) and treated with 85% potassium hydroxide (97 mg, 1.52 mmol) dissoved in methanol (5 ml) and stirred for 16 h. The mixture was treated with water (15 ml) and extracted with methylene chloride (2 x 25 ml). The organic layer was concentrated and chromatographed (2.5 x 10 cm, ethyl acetate) to give the chiral alcohol (266 mg) as an oil.

The lower ester fraction (260 mg, 0.40 mmol) was dissolved in methanol (5 ml) and treated with 85% potassium hydroxide (53 mg, 0.8 mmol) dissoved in methanol (5 ml) and stirred for 48 h. The mixture was treated with water (15 ml) and extracted with methylene chloride (2 x 25 ml). The organic layer was concentrated and chromatographed (2.5 x 10 cm, ethyl acetate) to give the chiral alcohol (154 mg) as an oil.

Balanol benzophenone (255 mg, 375 μmol) was dissolved in methylene chloride (3 ml) and treated with DMF (3 drops) followed by a 2M methylene chloride solution of oxalyl chloride (244 μL, 62 mg, 488 μmol). After stirring for 1 h, the mixture was concentrated and put under vacuum. The residue was dissolved in methylene chloride (5 ml) and added to chiral amidoalcohol (150 mg, 375 μmol), DMAP (5 mg), triethylamine (157 μL, 114 mg, 1.13 mmol) in methylene chloride (5 ml). After stirring for 16 h, the mixture was chromatographed directly (silica gel, 2.5 x 10 cm, 2/3 : ethyl acetate /hexanes) to give the ester (150 mg)as a glass. The glass was dissolved in 1/1 ethanol/methanol (10 ml), treated with trifluoroacetic acid (100 μL) and Pearlman's catalyst (palladium hydroxide, 15 mg) and stirred under a hydrogen atmosphere (balloon) for 16 h. The catalyst was filtered off and the mixture concentrated. The residue was chromatographed on a Dynamax®-60 C_{18} column (21 X 250 mm) using a linear gradient from 100% A (0.1% TFA and 5% acetonitrile in water) to 100% B (pure acetonitrile) over 60 m at 15 ml/min. The clean product, which eluted in 24 m., was concentrated to remove acetonitrile and freeze-dried to give a light yellow powder (45 mg, 22%), Compound 509, identical to Balanol by NMR, IR, CHN and analytical HPLC. Different rotation $[\alpha]_D^{25} = +97.8°$ (c = 0.319 in CH_3OH).

(-)-Trans-4-(4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydr xy benz yloxy)-3-(4-hydroxybenzamido)azepine Trifluoroacetic Acid Salt, (-)-Balanol (COMPOUND 510)



510

Trans-N-Benzyl-4(4-(6-benzyloxy-2-(benzyloxycarbonyl)benzoyl)-3,5-dibenzyloxybenzoyloxy)-3-(4-benzyloxybenzamido)azepine

A solution of 356 mg (0.583 mmol) of 4-(6-benzyloxy-2-(benzyloxycarbonyl)benzoyl)-3,5-dibenzyloxybenzoic acid in 10 ml of methylene chloride containing a trace (approximately 1 μL) of dimethylformamide was cooled to 0°C. A 2.0 M solution of oxalyl chloride (0.35 ml, 0.70 mmol) was added, and the mixture was stirred under a nitrogen atmosphere for 2 h. An additional 0.35 ml of oxalyl chloride was added, and the mixture was stirred for an additional 1 h. The reaction mixture was evaporated, and the residue was evaporated twice from 20 ml of methylene chloride. The residue was dissolved in 5 ml of methylene chloride, and was added to a solution of 251 mg (0.583 mmol) of trans-N-benzyl-3-(4-benzyloxybenzamido)-4-hydroxyazepine, 122 μL (0.700 mmol) of diisopropyl-

ethylamine, and 4.1 mg of DMAP in 9 ml of methylene chlorid at 0°C. The mixture was stirred at room temperature under a nitrogen atmosphere for 16 h, after which it was diluted with 75 ml of methylene chloride, washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated to give 690 mg of the crude product. Chromatography on silica gel eluting with 1/1 hexane - ethyl acetate gave 381 mg (60%) of the title compound as a yellow oil. IR (KBr) : 1719, 1655, 1605, 1581, 1456, 1321, 1248, 1111, 744, 697 cm-1. Anal. Calcd for $C_{70}H_{62}N_2O_{10}$•1.5 H_2O: C, 75.18; H, 5.86; N, 2.51. Found: C, 75.16; H, 5.88; N, 2.74.

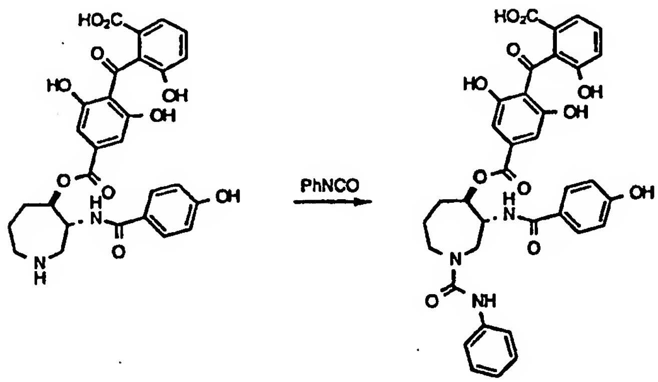
(-)-Trans-4-(4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxy benzoyloxy)-3-(4-hydroxybenzamido)azepine trifluoroacetic acid Salt (COMPOUND 510)

A solution of 363 mg (0.333 mmol) of trans-N-benzyl-4-(4-(6-benzyloxy-2-(benzyloxycarbonyl)benzoyl)-3,5-dibenzyloxybenzoyloxy)-3-(4-benzyloxybenzamido)azepine in 30 ml of ethanol was treated with 31 µL of trifluoroacetic acid, cooled to 0°C, and 53.3 mg of moist 10% palladium hydroxide on carbon was added. The mixture was stirred under an atmosphere of H_2 for 22 h. The mixture was filtered, evaporated, and the residue was chromatographed on a 41 x 250 mm C18 column (solvent A; 95:5 water/acetonitrile +0.1% TFA; solvent B: 100% acetonitrile; gradient: 0-50% B over 60 min, flow: 25 ml/min). The pure fractions were pooled and evaporated and then lyophilized from water to give 75.7 mg (32%) of Compound 510 as a yellow fluffy solid, together with an additional 69 mg (29%) of material which was 96% pure by NMR. mp>200 °C; $[\alpha]^{25}_D$ = -104° (c = 0.111, methanol); IR (KBr) : 1679, 1607, 1509, 1426, 1369, 1241, 1202, 763 cm^{-1}. Anal. Calcd for $C_{28}H_{26}N_2O_{10}$ • 3 H_2O • TFA: C, 50.14; H, 4.63, N, 3.90. Found: C, 50.11; H, 4.40; N, 4.01.

(±)-*anti*-3-(4-hydroxybenzamido)-4-[3,5-dihydroxy-4-(2-hydroxynaphthyl)carbonyl]benzoyl xyazepine trifluoroacetic acid salt (COMPOUND 511)

To (±)*anti*-3-(4-benzyloxybenzamido)-4-[3,5-dibenzyloxy -4-(2-benzyloxynaphthyl)carbonyl] benzoyloxy-N-benzylazepine (338 mg, 0.366 mmol) dissolved in absolute ethanol (18 ml) under an atmosphere of nitrogen was added trifluoracetic acid (30 µl, 0.386 mmol) followed by Pearlman's catalyst (135mg, 40 % by wt). An atmosphere of hydrogen was introduced and the mixture was allowed to stir for 48 h. The catalyst was removed by filtration and the volatiles removed under reduced pressure. The product was chromatographed on a Dynamax®-60 C18 column (41.4 mm ID X 30 cm length) using a linear gradient from 100% A (0.1% TFA and 5% acetonitrile in water) to 50% B (pure acetonitrile) over 60 m at 25 ml/min. The product elutes in 50 minutes. Removal of the volatiles provided Compound 511 as a yellow solid (99 mg, 38%), mp 165-168°C. IR KBr (disc) cm^{-1} 3397, 3274, 3121, 2874, 1796, 1776, 1680, 1633, 1606, 1544, 1510, 1461, 1426, 1369, 1344, 1202, 1142, 1109, 1054, 986, 910, 827, 802, 762, 723, 671. Anal. Calcd for $C_{31}H_{28}N_2O_7 \circ 2CF_3CO_2H$: C, 54.69; H, 3.93; N, 3.64. Found: C, 54.46; H, 4.06; N, 3.65.

Trans-4-(4-(2-Carboxy-6-hydr xybenzoyl)-3,5-dihydr xybenzoylo xy)-3-(4-hydroxybenzamido)-1-(phenylamin carb nyl)azepine (COMPOUND 512)



512

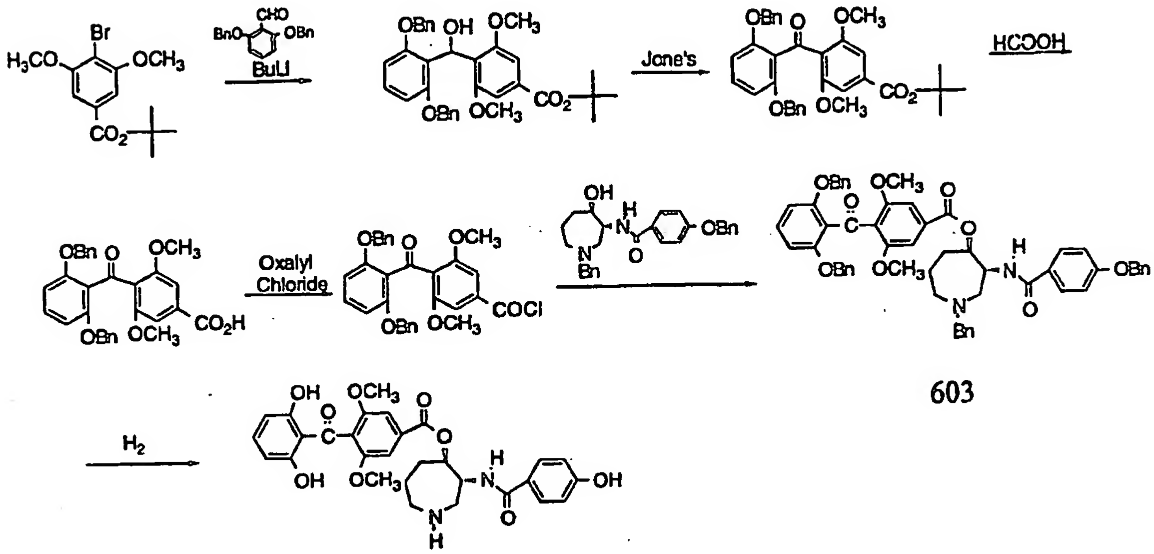
A solution of 25.2 mg (0.035 mmol) of (-)-trans-4-(4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy)-3-(4-hydroxybenzamido)azepine trifluoroacetic acid salt in 0.30 ml of dry pyridine was treated with 6.5 µL (7.1 mg, 0.060 mmol) of phenylisocyanate. The mixture was stirred for 3 h at room temperature, after which the reaction was quenched by the addition of 0.5 ml of methanol. The mixture was evaporated to a residue which was chromatographed on a 21 x 250 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0-100% B over 60 min, flow: 15 ml/min). The pure fractions were pooled and evaporated and then lyophilized from water to give 23.8 mg (95%) of Compound 512 as

a yellow fluffy solid, mp >200 °C. IR (KBr) : 1705, 1635, 1545, 1506, 1363, 1240, 760 cm^{-1}. Anal. Calcd for $C_{35}H_{31}N_3O_{11} \cdot 2.5 H_2O$: C, 58.82 H, 5.08; N, 5.88. Found: C, 59.04; H, 4.94; N, 5.77.

(±)-anti-3-(4-hydroxybenzamid)-4-[3,5-dihydr xy-4-(2,3,5,6-tetramethylphenyl)carbonyl]benzoyl xyazepine trifluoroacetic acid salt (COMPOUND 513)

To (±)-trans-3-(4-benzyloxybenzamido)-4-[3,5-dibenzyloxy-4-(2,3,5,6-tetramethylphenyl)carbonyl]benzoyloxy-N-benzylazepine (330 mg, 0.364 mmol) dissolved in 1:1 absolute ethanol:ethyl acetate (100 ml) under an atmosphere of nitrogen was added trifluoracetic acid (42 µl, 0.546 mmol) followed by Pearlman's catalyst (66 mg, 20 % by wt). An atmosphere of hydrogen was introduced and the mixture was allowed to stir for 24 h. The catalyst was removed by filtration and the volatiles were removed under reduced pressure. The product was chromatographed on a Dynamax®-60 C18 column (41.4 mm ID X 30 cm length) using a linear gradient from 100% A (0.1% TFA and 5% acetonitrile in water) to 50% B (pure acetonitrile) over 60 m at 25 ml/min. The product elutes in 58 minutes. Removal of the volatiles under reduced pressure provided Compound 513 as a yellow solid (185 mg, 75%), mp 157-160°C. IR KBr (disc) cm^{-1} 3084, 1717, 1682, 1637, 1609, 1559, 1542, 1509, 1474, 1457, 1425, 1375, 1339, 1270, 1234, 1199, 1140, 1108, 1076, 1007, 938, 848, 813, 767, 723, 669. Anal. Calcd for $C_{31}H_{28}N_2O_7$ • CF_3CO_2H • H_2O: C, 58.40; H, 5.50; N, 4.13. Found: C, 58.26; H, 5.28; N, 4.03.

(±)-Anti-4-[3,5-dimeth xy-4-(2,6-dihydroxyphenylcarbonyl)]-3-(4-hydroxybenzamido)perhydroazepine (COMPOUND 514)



603

514

The above compounds were synthesized using reactions indicated. Compound 514 was isolated as a yellow powder (37 mg, 5.2% overall yield): mp 165-175°C; NMR (D6 DMSO); IR (KBr) cm^{-1}: 3431 (OH); 1710 (ester); 1625 (ketone). Anal. calc. for $C_{29}H_{30}N_2O_9 \cdot 1.5\ H_2O$: C, 60.31; H, 5.76; N, 4.85. Found: C, 60.53; H, 5.85; N, 4.91. Intermediate Compound 603 was also isolated.

***syn*-4-(4-(2-Carb xy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyl-amino)hexahydr -3-(4-hydr xybenz ylamino)azepine, trifluoro-ac tic acid salt (COMPOUND 516)**

Hexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethyl-azepin 4-one

A 25 ml 3-neck round bottom flask under nitrogen was charged with 2.0 N oxalyl chloride/methylene chloride (Aldrich, 1.125 ml, 2.25 mmol), diluted with anhydrous methylene chloride (2 ml), cooled (-65°C), and treated dropwise with anhydrous dimethylsulfoxide (0.35 g, 4.5 mmol) in anhydrous methylene chloride (1.2 ml) at a rate to keep the pot temperature below -60°C. The mixture was stirred at -65 ± 5°C for 30 min, then treated dropwise with a solution of syn-hexahydro-4-hydroxy-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.645 g, 1.5 mmol) in anhydrous methylene chloride (1.5 ml) at a rate to keep the pot temperature below -55°C. The mixture was stirred at 55±5°C for 2 h, then treated dropwise with triethylamine (1.5 ml), warmed to room temperature over one hour, and diluted with methylene chloride (10 ml). The organic solution was washed with water (10 ml), saturated aqueous sodium bicarbonate (10 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed on silica gel (eluted with 5% acetone/ methylene chloride) to afford hexahydro-3-(4-phenyl-methoxy) benzoylamino-1-phenylmethylazepin-4-one (0.53 g, 82%) as a viscous colorless oil.

Hexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethyl-azepin-4-one, oxime

A solution of hexahydro-3-(4-phenylmethoxy)-benzoylamino-1-phenylmethyl-azepin-4-one (0.87 g, 2.03 mmol) in ethanol (12 ml) was treated with hydroxylamine hydrochloride (0.19 g, 2.73 mmol), followed by 25% methanolic sodium methoxide (Aldrich, 0.20 g, 0.93 mmol), and was heated to 50°C for one hour. The mixture was cooled to room temperature and treated with additional 25% methanolic sodium methoxide (0.42 g, 1.94 mmol), then concentrated *in vacuo* to afford hexahydro-

3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepin-4-one oxime (0.89 g, 99%) as a colorless foam.

syn-4-(3,5-Bis(phenylmethoxy)-4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)benzoylaminohexahydro-3-(4-phenylmethoxy)-benzoylamino-1-phenylmethylazepine (COMPOUND 615)

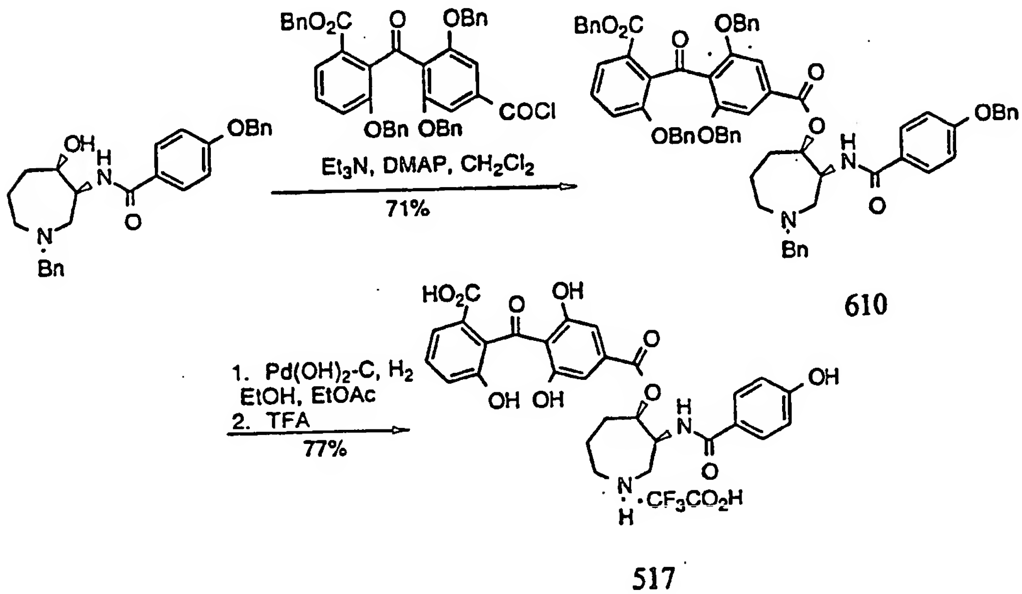
A solution of hexahydro-3-(4-phenylmethoxy)-benzoyl amino-1-phenylmethyl-azepin-4-one oxime (0.40 g, 0.90 mmol) in reagent methanol (25 ml) in a Parr bottle was treated with Raney Nickel (Aldrich, quarter tsp.), then subjected to hydrogenation at 49-50 psi for six hours. The solution was carefully evacuated of hydrogen, filtered through celite, and the filtrate was concentrated *in vacuo* to afford 4-aminohexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenyl methylazepine, 1:1 mixture of isomers, which was kept under nitrogen. Meanwhile, 2'-carbobenzyloxy-2,6,6'-tribenzyloxy benzophenone-4-carboxylic acid (SPC-104034, 0.37 g, 0.55 mmol) was placed in a round-bottom flask and repeatedly covered with toluene and concentrated *in vacuo* to remove all water and other persistent solvents. Finally, the residue was dissolved in anhydrous methylene chloride (2 ml) under nitrogen, treated with dimethylformamide (3 drops), then with 2.0 N oxalyl chloride/methylene chloride (0.4 ml, 0.8 mmol), and stirred at room temperature for one hour. The solution was concentrated *in vacuo*, placed under high vacuum for one hour, then dissolved in methylene chloride (3 ml) and added to the 4-aminohexahydro-3-(4-phenylmethoxy)-benzoylamino-1-phenylmethylazepine prepared above. Sodium hydroxide (1.0 N, 1.5 ml) was added, and the mixture was stirred for one hour and separated. The aqueous layer was extracted with methylene chloride (2x10 ml), and the combined organic layer and extracts were washed with saturated sodium chloride (10 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed (flash) on silica gel (eluted successively with 3% acetone/methylene chloride, 5% acetone/methylene chloride, and 8% acetone/methylene chloride) to afford, initially, *syn*-4-(3,5-bis(phenylmethoxy)-4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)-benzoylamino

hexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethyl-azepine (0.26 g, 43%), then *anti*-4-(3,5-bis(phenylmethoxy)-4-(2-carbophenyl-methoxy-6-phenylmethoxybenzoyl)benzoylamino hexahydro-3-(4-phenyl-methoxy)benzoylamino-1-phenylmethyl azepine (0.21 g, 35%) as colorless foams. The combined yield was 0.47 g (78%).

syn-4-(4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyl-amino)hexahydro-3-(4-hydroxybenzoylamino)azepine, trifluoro-acetic acid salt (COMPOUND 516)

A solution of *anti*-4-(3,5-bis(phenylmethoxy)-4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)benzoylaminohexahydro -3-(4-phenylmethoxy)-benzoylamino-1-phenylmethylazepine (0.20 g, 0.183 mmol) in reagent ethanol (9 ml) and ethyl acetate (1 ml) in a 2-neck 25-ml round bottom flask under nitrogen was treated with Pearlman's catalyst (20% $Pd(OH)_2/C$, 50 mg) and trifluoroacetic acid (42 mg, 0.37 mmol). The flask was fitted with a balloon and a balloon valve, purged with hydrogen, and placed under positive hydrogen pressure for 18 h, then evacuated of hydrogen and purged for several minutes with nitrogen. The solution was carefully filtered through celite (wash filter pad with ethanol) and the filtrate was concentrated *in vacuo* to a yellow foam. This was dissolved in methanol (20 ml), diluted with deionized water (60 ml), and concentrated *in vacuo* to remove the methanol. Freeze drying (without chromatography) afforded *syn*-4-(4-(2-carboxy-6-hydroxy benzoyl)-3,5-dihydroxybenzoylamino)hexahydro-3-(4-hydroxy benzoylamino)azepine (94 mg, 68%) as a voluminous yellow solid; mp >300°C(dec). Rf (4% acetic acid/ethanol) 0.50; IR (KBr) 1683, 1636, 1604 cm^{-1}; ^1H NMR (d_6-DMSO) δ 11.66 (s, 2H), 10.07 (s, 1H), 9.86 (s, 1H), 8.60 - 9.00 (br s, 2H), 8.33 (d, 1H, J = 8 Hz), 8.00 (d, 1H, J = 7 Hz), 7.70 (d, 2H, J = 9 Hz), 7.37 (d, 1H, J = 8 Hz), 7.27 (t, 1H, J = 8 Hz), 7.06 (d, 1H, J = 8 Hz), 6.82 (d, 2H, J = 9 Hz), 6.68 (s, 2H), 4.55 (m, 1H), 4.40 (m, 1H), 3.10 - 3.50 (m, 4H), 1.70 - 2.10 (m, 4H). Anal. Calcd. for $C_{28}H_{27}N_3O_9 \cdot 1.5(C_2HO_2F_3) \cdot 2.0(H_2O)$: C, 49.21; H, 4.33; N, 5.55. Found: C, 48.82; H, 4.59; N, 5.79.

syn-4-[4-(2-hydroxycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxy benz yl xy]-3-(4-hydroxybenzamido)perhydroaz pine trifluoroacetic acid salt (COMPOUND 517)



COMPOUND 610

To a chilled solution (0-5 °C) of 4-(6-benzyloxy-2-(benzyloxycarbonyl)benzoyl)-3,5-dibenzyloxybenzoic acid (0.52 mmol, 350 mg) in 2 ml of methylene chloride under nitrogen atmosphere was added oxalyl chloride (0.75 mmol, 95 mg) in one portion. N,N-Dimethylformamide (1 drop) was added and the light brown solution was stirred at 0 °C for 1.5 h. The solvent and excess oxalyl chloride were then removed *in vacuo*, the resulting brown oil was redissolved in methylene chloride (2 ml) and added to a cooled solution (0-5 °C) of *syn*-N-benzyloxycarbonyl-3-(4-hydroxybenzamido)-4-hydroxyperhydroazepine (0.62 mmol, 226 mg), triethylamine (1.29 mmol, 130 mg) and 4-dimethylaminopyridine (approximately 10 mg) in 2 ml methylene chloride (nitrogen atmosphere). The reaction mixture was allowed to warm to room temperature and

stirred overnight (approximately 18 h) under a nitrogen atmosphere, after which it was diluted with 50 ml of methylene chloride, washed with saturated sodium bicarbonate solution (10 ml), water (10 ml), and brine (10 ml), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give 440 mg of the crude product. Chromatography on silica gel eluting with 4:1-hexane:ethyl acetate gave 399 mg (71%) of the coupled product as a light yellow solid, which was used directly in the next step.

To a solution of *syn*-N-benzyloxycarbonyl-4-[4-(2-benzyloxycarbonyl-6-benzyloxybenzoyl)-3,5-dibenzyloxy benzoyloxy]-3-(4-benzyloxybenzamido)perhydroazepine (0.16 mmol, 180 mg) in ethyl acetate (5 ml) and absolute ethanol (10 ml) was added moist 20% palladium hydroxide on carbon (20% w/w, 36 mg). The reaction flask was fitted with a hydrogen balloon and the grey suspension was stirred at room temperature for 18 hours. The reaction flask was then purged with nitrogen gas and the solution diluted with chloroform (50 ml), filtered over celite, treated with 1 ml of trifluoroacetic acid, and concentrated *in vacuo* to give 87 mg of the crude product. The material was purified by HPLC chromatography with a 21 x 250 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient 0-50% B over 60 minutes, flow: 15 ml/min). The purified fractions were concentrated and lyophilized from water to give 67 mg (63%) of the title compound as a yellow fluffy solid. IR (KBr): 1704, 1688, 1677, 1632, 1608, 1427, 1235, 1201 cm^{-1}; EA (calculated for $C_{28}H_{26}N_2O_{10}\cdot 1.2\ C_2HF_3O_2\cdot 2.0\ H_2O$): C, 50.48; H, 4.35; N, 3.87. Found: C, 50.51; H, 4.46; N, 3.88.

(±)-*anti*-3-(4-hydroxybenzamido)-4-[3,5-dimethoxy-4-(2,6-dimethoxy)benzoyl]benzoyloxylperhydroazepine trifluor ac tic acid salt (COMPOUND 518)

To (±)-*anti*-3-(4-benzyloxybenzamido)-4-[3,5-dimethoxy-4-(2,6-dimethoxy)benzoyl]benzoyloxy-N-benzylperhydroazepine (221 mg, 0.291 mmol) dissolved in ethyl acetate (50 ml) under an atmosphere of nitrogen was added trifluoracetic acid (35 μL, 0.437 mmol) followed by Pearlman's catalyst (44 mg, 20 % by wt on carbon). An atmosphere of hydrogen was introduced and the mixture allowed to stir for 48 h. The catalyst was removed by filtration and the volatiles were removed under reduced pressure. The product was chromatographed on a Dynamax®-60 C18 column (41.4 mm ID X 30 cm length) using a linear gradient from 100% A (0.1% TFA and 5% acetonitrile in water) to 100% B (pure acetonitrile) over 60 m at 25 ml/min. The product elutes in 58 minutes. Removal of the volatiles under reduced pressure provided Compound 518 as a white solid (62 mg, 26%), mp 134-137°C. IR KBr (disc) cm^{-1} 3430, 3105, 3016, 2948, 2843, 1772, 1677, 1592, 1544, 1508, 1474, 1436, 1411, 1331, 1235, 1203, 1182, 1127, 1111, 950, 917, 848, 798, 766, 720, 620, 602. Anal. Calcd for $C_{31}H_{34}N_2O_9 \circ 2CF_3CO_2H$: C, 52.11; H, 4.50; N, 3.47. Found: C, 52.30; H, 4.50; N, 3.47.

(±)-anti-3-(4-benzyloxybenzamido)-4-[3,5-dimethoxy-4-(2,6-dimethoxy)benzoyl]benzoyloxy-N-benzylperhydroazepine (COMPOUND 604)

To a solution of 3,5-dimethoxy-4-(2,6-dimethoxybenzoyl)benzoic acid (221 mg, 0.639 mmol) in anhydrous dichloromethane (10 ml) under an atmosphere of nitrogen at 0°C was added oxalyl chloride (436 μL, 2 M in dichloromethane, 0.872 mmol) dropwise over 5 minutes followed by anhydrous dimethylformamide (3 drops). The ice bath was removed and the suspension rapidly turned into a clear yellow solution. The reaction mixture was allowed to stir for 0.5 h at room temperature. The volatiles were removed under reduced pressure and the remaining solid was dried under vacuum for 2.5 h.

To a solution of (±)-*anti*-3-(4-benzyloxybenzamido)-4-hydroxy-N-benzylperhydroazepine (250 mg, 0.581 mmol), triethylamine (267 µL, 1.92 mmol), and dimethylaminopyridine (7.1 mg, 0.0581 mmol) in anhydrous dichloromethane (10 ml) under an atmosphere of nitrogen at 0°C was added a solution of the above generated acid chloride in anhydrous dichloromethane (10 ml) dropwise over 0.5 h. After allowing to stir while warming to room temperature overnight the reaction mixture was diluted with dichloromethane (200 ml) and washed with water (75 ml). The dichloromethane layer was dried over magnesium sulfate, filtered, and the volatiles were removed under reduced pressure to give a crude white solid. The solid was purified using flash column chromatography (silica gel, 9 : 1 dichloromethane and ethyl acetate) to provide Compound 604 as a white solid (266 mg, 60%), mp 82-85°C. IR KBr (disc) cm^{-1} 3481, 3029, 2939, 2837, 1711, 1676, 1644, 1591, 1530, 1498, 1474, 1407, 1327, 1248, 1177, 1111, 1024, 995, 913, 845, 795, 744, 700, 605. Anal. Calcd for $C_{45}H_{46}N_2O_8$: C, 71.22; H, 6.11; N, 3.69. Found: C, 71.08; H, 6.15; N, 3.64.

3,5-dimethoxy-4-(2,6-dimethoxy)benzoylbenzoic acid

To t-butyl-3,5-dimethoxy-4-(2,6-dimethoxybenzoyl) benzoate (2.26 g, 5.62 mmol) under an atmosphere of nitrogen at 0°C was added formic acid (25 ml) dropwise. The ice bath was removed and the reaction mixture was allowed to stir at room temperature for 8 h. The volatiles were removed under reduced pressure. Recrystallization of the crude solid with 1:1 ethyl acetate:hexanes provided the title compound as a white solid (1.69 g , 87%), mp 209-212°C. ^1H NMR (DMSO-d_6) δ 7.32 (t, 1 H, J = 8 Hz), 7.16 (s, 2 H), 6.64 (d, 2 H, J = 8 Hz), 3.67 (s, 6 H), 3.61 (s, 6 H); IR KBr (disc) cm^{-1} 3432, 3199, 3103, 3016, 2936, 2838, 1731, 1653, 1589, 1475, 1429, 1409, 1313, 1258, 1222, 1185, 1128, 1113, 1028, 944, 897, 869, 801, 773, 713, 690, 617. Anal. Calcd for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24. Found: C, 62.43; H, 5.30.

t-butyl-3,5-dimethoxy-4-(2,6-dimethoxybenz yl)benz ate

To a solution of t-butyl-3,5-dimethoxy-4-[(2,6-dimethoxyphenyl)hydroxymethyl]benzoate (3.10 g, 7.70 mmol) in acetone (50 ml) at 0°C was added Jones reagent dropwise until the reaction mixture retained the orange color of the Jones reagent. The reaction mixture was diluted with dichloromethane (500 ml) and washed with water (150 ml). The dichloromethane layer was dried over anhydrous magnesium sulfate, filtered and the volatiles were removed under reduced pressure. The crude residue was purified using flash column chromatography (silica gel, 1 : 8 ethyl acetate / hexane) to provide the title compound as white solid (2.36 g, 88%), mp 54-57°C. ^{1}H NMR (DMSO-d_6) δ 7.32 (t, 1 H, J = 8.5 Hz), 7.11 (s, 2 H), 6.63 (d, 2 H, J = 8.5 Hz), 3.67 (s, 6 H), 3.61 (s, 6 H) 1.55 (s, 9 H); IR KBr (disc) cm^{-1} 2974, 2839, 1711, 1685, 1590, 1473, 1434, 1406, 1369, 1330, 1292, 1253, 1163, 1126, 1111, 1032, 957, 915, 849, 796, 765, 705, 669, 610. Anal. Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found: C, 65.67; H, 6.49.

t-butyl-3,5-dimethoxy-4-[(2,6-dimethoxyphenyl)hydroxymethyl]benzoate

To a solution of t-butyl-3,5-dimethoxy-4-bromobenzoate (3.50 g, 11.0 mmol) in anhydrous tetrahydrofuran (60 ml) under an atmosphere of nitrogen with an internal temperature of -78°C (ether/dry ice) was added n-butyllithium (7.58 ml, 1.6 M in hexanes, 12.1 mmol) dropwise at a rate which did not allow the internal temperature to rise above -65°C. To the reaction mixture was added a solution of 2,6-dimethoxybenzaldeyde (1.83 g, 12.1 mmol) in anhydrous tetrahydrofuran (20 ml) dropwise at a rate which did not allow the internal temperature to rise above -65°C. The reaction mixture was allowed to stir while warming to room temperature over 2 h. The reaction mixture was quenched with solid ammonium chloride and the volatiles were removed under reduced pressure. The crude residue was diluted with ethyl acetate (500 ml) and washed with water (200 ml). The ethyl acetate layer was dried over anhydrous magnesium sulfate, filtered, and the volatiles were removed under reduced pressure. The crude residue was purified by recrystallization

from 1 : 1 ethyl acetate : hexane which provided a white solid of the title compound (3.2 g, 72%), mp 131-133°C. ^{1}H NMR (DMSO-d_6) δ 7.14 (t, 1 H, J = 8.5 Hz), 7.08 (s, 2 H), 6.58 (d, 2 H, J = 8.5 Hz), 6.43 (d, 1 H, J = 10.5 Hz), 5.37 (d, 1 H, J = 10.5 Hz) 3.76 (s, 6 H), 3.70 (s, 6 H) 1.63 (s, 9 H);IR KBr (disc) cm^{-1} 3541, 3445, 2978, 2843, 1701, 1651, 1588, 1542, 1477, 1455, 1417, 1366, 1328, 1241, 1161, 1119, 1030, 958, 847, 809, 770, 667. Anal. Calcd for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.19; H, 6.99.

t-butyl-4-bromo-3,5-dimethoxybenzoate

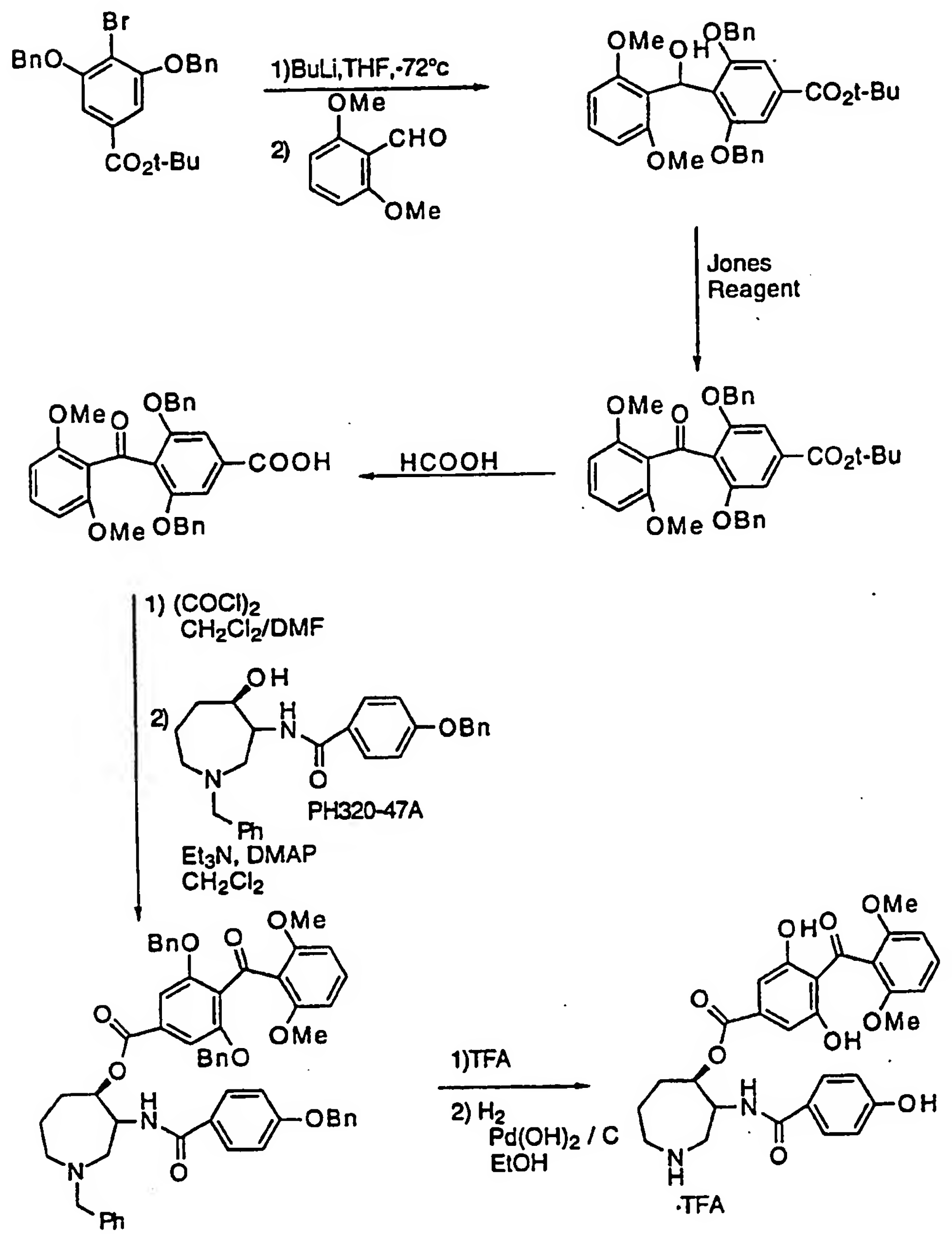
To a solution of 4-bromo-3,5-dimethoxybenzoic acid (9.20 g, 35.2 mmol) in anhydrous dimethylformamide (200 ml) under an atmosphere of nitrogen was added N,N-carbonyl diimidazole (6.29 mg, 38.8 mmol). After the reaction mixture was allowed to stir for 1 h at room temperature, DBU (5.80 ml, 38.8 mmol), and t-butanol (9.97 ml, 106 mmol) were added. The reaction mixture was heated at 80°C for 2 h. The reaction mixture was quenched by the slow addition of water (300 ml). The solid which formed was collected by suction filtration and washed with water (3 X 30 ml) which provided the title compound as a white solid (5.8 g, 52%), mp 119-121°C. ^{1}H NMR (DMSO-d_6) δ 7.17 (s, 2 H), 3.89 (s, 6 H), 1.57 (s, 9 H); IR KBr (disc) cm-1 2979, 2936, 2836, 1708, 1590, 1456, 1408, 1366, 1337, 1258, 1231, 1174, 1124, 1033, 960, 857, 798, 761, 643. Anal. Calcd for $C_{13}H_{17}BrO_4$: C, 49.23; H, 5.40. Found: C, 49.05; H, 5.36.

4-bromo-3,5-dimethoxybenzoic acid

To methyl 4-bromo-3,5-dimethoxybenzoate (10 g, 36.4 mmol, Pharmatech International) was added sodium hydroxide (75 ml, 10 N) and methanol (50 ml). The reaction mixture was heated at 70°C for 1.5 h. The reaction mixture was cooled to 0°C and slowly acidified using HCl (6N). The solid was collected by suction filtration to provide a white solid of the title compound (9.31 g, 98%), mp 225-228°C. ^{1}H NMR (DMSO-d_6) δ 13.3 (br s, 1 H), 7.23 (s, 2 H), 3.90 (s, 6 H); IR KBr

(disc) cm^{-1} 3400, 3064, 2969, 2838, 2745, 1689, 1586, 1461, 1407, 1329, 1276, 1230, 1189, 1127, 1039, 935, 857, 764, 730, 667, 639. Anal. Calcd for $C_8H_9BrO_4$: C, 41.41; H, 3.47. Found: C, 41.44; H, 3.40.

(3R,4R)-[4-(2,6-Dimethoxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxyb nzamido)perhydroazepine triflu roacetic acid salt (COMPOUND 519)



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519

1,1-Dimethylethyl 3,5-dibenzyloxy-4-[(2,6-dimethoxyphenyl)-hydroxymethyl) benzoate

2.5 ml (7.02 mmole) of 2.5 M n-butyllithium in hexane was added dropwise to a cold solution (-72°C) of t-butyl-4-bromo-3,5-dibenzyloxybenzoate (2.69 g, 5.47 mmole) in 40 ml of anhydrous tetrahydrofuran (THF) under nitrogen. The temperature of the solution was maintained below -70°C throughout the addition and the solution was stirred in the cold for ten minutes. A solution of 1 g (6.02 mmole) of 2,6-dimethoxybenzaldehyde in 15 ml of THF was added dropwise maintaining the temperature below -65°C throughout the addition. The solution was allowed to warm to room temperature as it stirred for two hours. The solution was partitioned between 20 ml of 1 N hydrocholoric acid and 50 ml of ethyl acetate while stirring fifteen minutes. The organic layer was separated, washed with water, saturated brine and dried over magnesium sulfate. The solvent was removed in vacuo. The residue was recrystallized from ethyl acetate-hexane to give 0.83 g (26%) of the title compound as white crystals, mp 152-155°C. Anal. Calcd for $C_{34}H_{36}O_7$: C, 73.36; H, 6.51. Found: C, 73.04; H, 6.54.

1,1-Dimethylethyl 4-(2,6-dimethoxybenzoyl)-3,5-dibenzoyl oxybenzoate

To a cold solution (0°C) of 0.7 g (1.25 mmole) of 1,1-dimethylethyl 3,5-dibenzyloxy-4-[(2,6-dimethoxyphenyl)-hydroxymethyl) benzoatein 15 ml of acetone was added 4 ml of Jones reagent. The solution was stirred in the cold for two hours. To the solution was added 10 ml of isopropyl alcohol to destroy the Jones reagent. The reaction mixture was filtered through celite and washed through with acetone. The filtrate was concentrated in vacuo. The residue was recrystallized from ethanol-water to yield 0.47 g (68%) of the title compound as tan crystals. Anal. Calcd for $C_{34}H_{34}O_7$: C, 73.63; H, 6.18. Found: C, 73.15; H, 6.38.

4-(2,6-Dimethoxybenzoyl)-3,5-dibenzyloxybenzoic acid

A solution of 0.46 g (0.83 mmole) of 1,1-dimethylethyl 4-(2,6-dimethoxybenzoyl)-3,5-dibenzyloxybenzoate in 10 ml of formic acid was stirred at room temperature for two hours. After stirring for one hour a precipitate formed. The reaction mixture was poured over ice water, and the resultant precipitate was collected and dried to yield 0.36 g (87%) of a tan solid.

Trans-N-Benzyl-4-(4-(2,6-dimethoxybenzoyl)-3,5-dibenzyloxy)-3-(4-benzyloxybenzamido)azepine (COMPOUND 605)

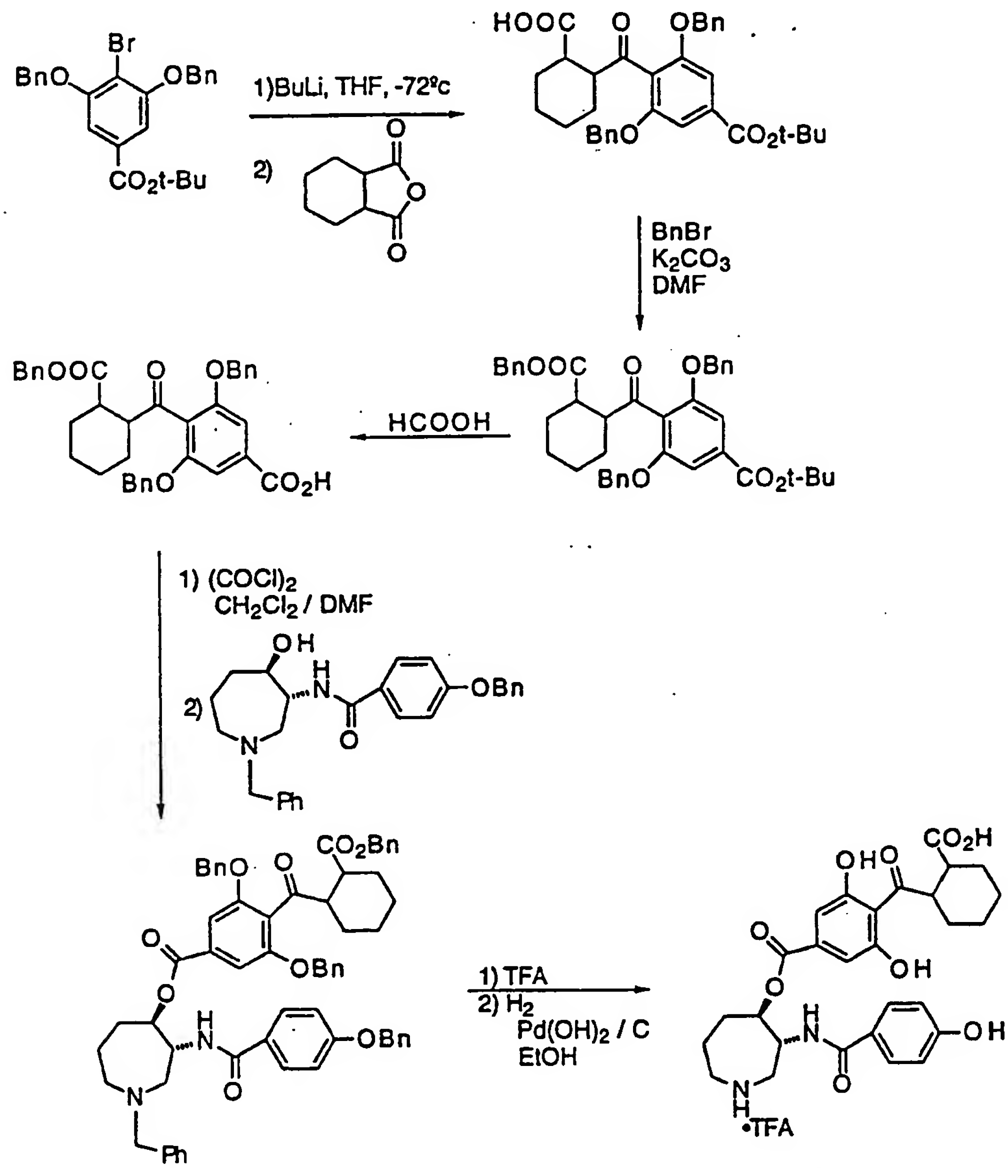
A solution of 0.36 g (0.72 mmole) of 4-(2,6-dimethoxybenzoyl)-3,5-dibenzyloxybenzoic acid in 10 ml of methylene chloride containing a trace (approximately 1 μL) of dimethylformamide was cooled to 0°C. A 2.0 M solution of oxalyl chloride in methylene chloride (0.41 ml, 0.82 mmole) was added, and the mixture was stirred under a nitrogen atmosphere for ninty minutes. The reaction mixture was evaporated and the residue was evaporated twice from 15 ml of methylene chloride. The residue was dissolved in 8 ml of methylene chloride and was added to a solution of 0.35 g (0.82 mmole) of trans-N-benzyl-3-(4-benzyloxybenzamido)-4-hydroxyazepine, 0.06 ml (0.82 mmole) triethylamine, and 4.0 mg of DMAP in 10 ml of methylene chloride. The solution was stirred at room temperature under nitrogen for sixteen hours. The solution was diluted with 30 ml of methylene chloride and washed with saturated sodium bicarbonate, saturated brine, dried over magnesium sulfate, and the solvent was removed in vacuo. The residue was chromatographed on silica gel eluting with hexane-ethyl acetate (70:30). Yield 0.33 g (43%) of a glassy oil which solidified on standing.

(3R,4R)-[4-(2,6-Dimethoxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)perhydroazepine trifluoroacetic acid salt (COMPOUND 519)

A solution of 0.33 g (0.36 mmole) of trans-N-benzyl-4-(4-(2,6-dimethoxybenzoyl)-3,5-dibenzoyloxy)-3-(4-benzyloxy

benzamido)azepine in 20 ml ethanol-methylene chloride (1:1) was treated with 0.055 ml (0.720 mmole) of trifluoroacetic acid. The solution was stirred for five minutes. The solvent was evaporated. The ethanol-methylene chloride solvent was added twice more and evacuated in order to remove excess trifluoroacetic acid. The residue was taken up in 15 ml of ethanol, cooled to 0°C, and 0.5 g of moist 10% palladium hydroxide on carbon was added. The mixture was then stirred under an atmosphere of hydrogen for six hours at room temperature. The mixture was filtered, evaporated, and the residue was chromatographed on a 41 X 250 mm C 18 column (solvent A: 95 : 5 water / acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient : 0 - 50% B over 60 min., flow: 25 ml / min.). The pure fractions were pooled and evaporated to yield 0.158 g (60%) of Compound 519, a yellow powder, mp 189-193 °C. IR (KBr); 1678, 1605, 1508, 1427, 1370, 1250, 1200, 765 cm^{-1}. Anal. Calcd for $C_{29}H_{30}N_2O_8$ • $2H_2O$ B 1.3 TFA: C, 51.65; H, 4.84: N, 3.81. Found: C, 51.27; H, 4.68; N, 3.62.

Trans-4-(4-(2-cis-carb xycyclohexylcarbonyl)-3,5-dihydroxybenzoyl xy)-3-(4-hydroxybenzamido) azepine trifluoroacetic acid salt (COMPOUND 519)



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520

1,1-Dimethylethyl 3,5-dibenzyloxy-4-(2-cis-carboxycyclohexylcarbonyl) benzoate

2.8 ml (7.03 mmole) of 2.5 N n-butyllithium in hexane was added dropwise to a cold solution (-72 °C) of 3.0 g (6.39 mmole) of 1,1-dimethylethyl 4-bromo-3,5-dibenzyloxybenzoate in

40 ml of anhydrous tetrahydrofuran (THF) under nitrogen. The solution was stirred in the cold for ten minutes. A solution of 1.2 g (7.03 mmole) of cis-1,2-cyclohexanedicarboxylic anhydride in 10 ml of THF was added dropwise maintaining the temperature below -70 °C. The solution was stirred in the cold for two hours. The solution was poured into 150 ml of saturated ammonium chloride and 350 ml of ether. The reaction mixture was stirred for thirty minutes. The organic layer was separated, washed with 0.1 N hydrochloric acid, saturated brine and dried over magnesium sulfate. The solvent was evaporated to yield 3.4 g (98 %) of a clear oil.

1,1-Dimethylethyl 4-(4-(2-cis-benzyloxycyclohexylcarbonyl))-3,5-dibenzyloxybenzoate

To a solution of 3.40 g (6.20 mmole) of 1,1-dimethylethyl 3,5-dibenzyloxy-4-(2-cis-carboxycyclohexylcarbonyl)benzoate in 20 ml of dry DMF was added 0.43 g (3.10 mmole) of potassium carbonate and 0.33 ml (3.10 mmole) of benzyl bromide. The solution was stirred at room temperature under nitrogen for eight hours. Starting material was still present in the reaction. Therefore, an additional 0.16 ml (1.5 mmole) of benzyl bromide was added and stirring was continued for sixteen hours. The solution was poured over 100 ml of ice water, extracted twice with 150 ml portions of ether. The ether solution was washed with water, saturated brine and dried over magnesium sulfate. The solvent was evaporated and the residue was chromatographed on silica gel eluting with 5 % - 10 % ethyl acetate - hexane to yield 1.0 g (25 %) of a clear oil.

4-(4-(2-cis-benzyloxycyclohexylcarbonyl)-3,5-dibenzyloxybenzoic acid

A solution of 0.45 g (0.71 mmole) of 1,1-dimethylethyl 4-(4-(2-cis-benzyloxycyclohexylcarbonyl)-3,5-dibenzyloxybenzoate in 10 ml of formic acid was stirred at room temperature for four hours. The solution was poured over ice water, the resultant precipitate was collected and dried to yield 0.34 g (82.8%) of a white solid. Anal. Calcd for $C_{36}H_{34}O_7$: C, 74.72 ; H, 5.92. Found : C, 74.46 ; H,5.99.

Trans-N-benzyl-4-(4-(2-cis-benzyloxycyclohexylcarbonyl)-3-(4-benzyl xybenzamido)azepin (COMPOUND 606)

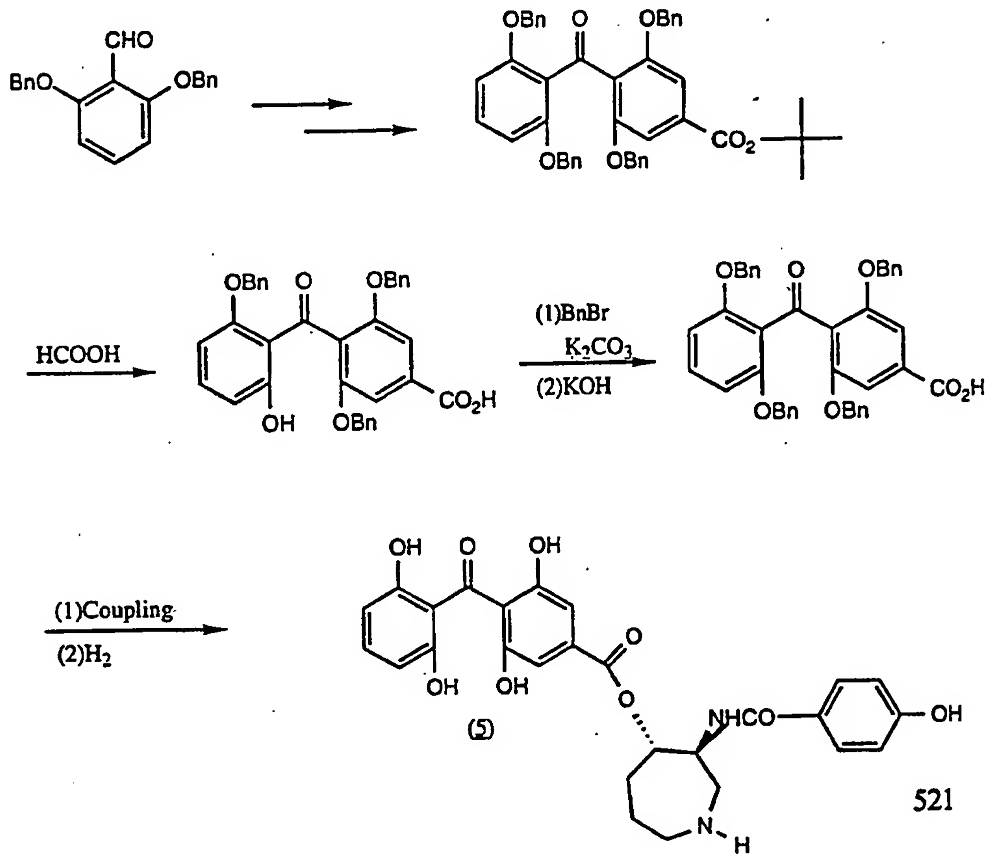
A solution of 0.40 g (0.69 mmole) of 4-(4-(2-cis-benzyloxycyclohexylcarbonyl)-3,5-dibenzyloxybenzoic acid in 8 ml of methylene chloride containing a trace (amount approximately 1 μL) of dimethylformamide was cooled to 0 °C. A 2.0 M solution of oxalyl chloride in methylene chloride (0.59 ml, 1.18 mmole) was added and the solution was stirred under nitrogen for 2.5 hours. The reaction mixture was evaporated, and the residue was evaporated twice from 15 ml of methylene chloride. The residue was dissolved in 8 ml of methylene chloride and added to a solution of 0.34 g (0.78 mmole) of trans-N-benzyl-3-(4-benzyloxybenzamido)-4-hydroxyazepine, 0.08 ml (0.78 mmole) of triethylamine and 4.0 mg of DMAP in 10 ml of methylene chloride. The solution was stirred at room temperature under nitrogen for sixteen hours. The solution was diluted with 30 ml of methylene chloride and washed with saturated sodium bicarbonate, saturated brine and dried over magnesium sulfate. The solvent was evaporated and the residue was chromatographed on silica gel eluting with ethyl acetate-hexane (1:4). Yield of 0.5 g (73%) of a clear oil.

Trans-4-(4-(2-cis-carboxycyclohexylcarbonyl)-3,5-dihydroxybenzyloxy)-3-(4-hydroxybenzamido)azepine trifluoroacetic acid salt (COMPOUND 520)

A solution of 0.38 g (0.38 mmole) of trans-N-benzyl-4-(4-(2-cis-benzyloxycyclohexylcarbonyl))-3-(4-benzyloxybenzamido)azepine in a 25 ml mixture of methanol, ethanol and methylene chloride (1 : 2 : 2) was treated with 0.06 ml (0.77 mmole) of trifluoroacetic acid for five minutes. The solvent was evaporated, and the methanol, ethanol, methylene chloride solvent was added twice more and evaporated. The residue was taken up in 15 ml of ethanol, cooled to 0 °C and 0.05 g of palladium hydroxide on carbon (20% by wt.) was added. The mixture was then stirred under an atmosphere of hydrogen for six hours at room temperature. The mixture was filtered, evaporated and the residue was chromatographed on a

41 X 250 mm C18 column (solvent A: 95 : 5 water / acetonitrile + 0.1% TFA; solvent B : 100% acetonitrile ; gradient 0 - 50% B over 60 min., flow 25 ml / min.). The pure fractions were pooled to yield 57 mg (21%) of a yellow powder, mp 122 - 127 °C. IR (KBr) : 1676, 1607, 1508, 1427, 1365, 1276, 1203, 757 cm^{-1}. Anal. Calcd for $C_{28}H_{32}N_2O_9 \circ 2H_2O \circ 1.2$ TFA : C, 51.18 ; H, 5.25 ; N, 3.92. Found : C, 51.46 ; H, 5.37 ; 3.92.

(+)-*Anti*-4-[3,5-dihydroxy-4-(2,6-dihydroxybenzoyl)]hexahydro-3-(4-hydroxybenzoylamine)azepin (COMPOUND 521)

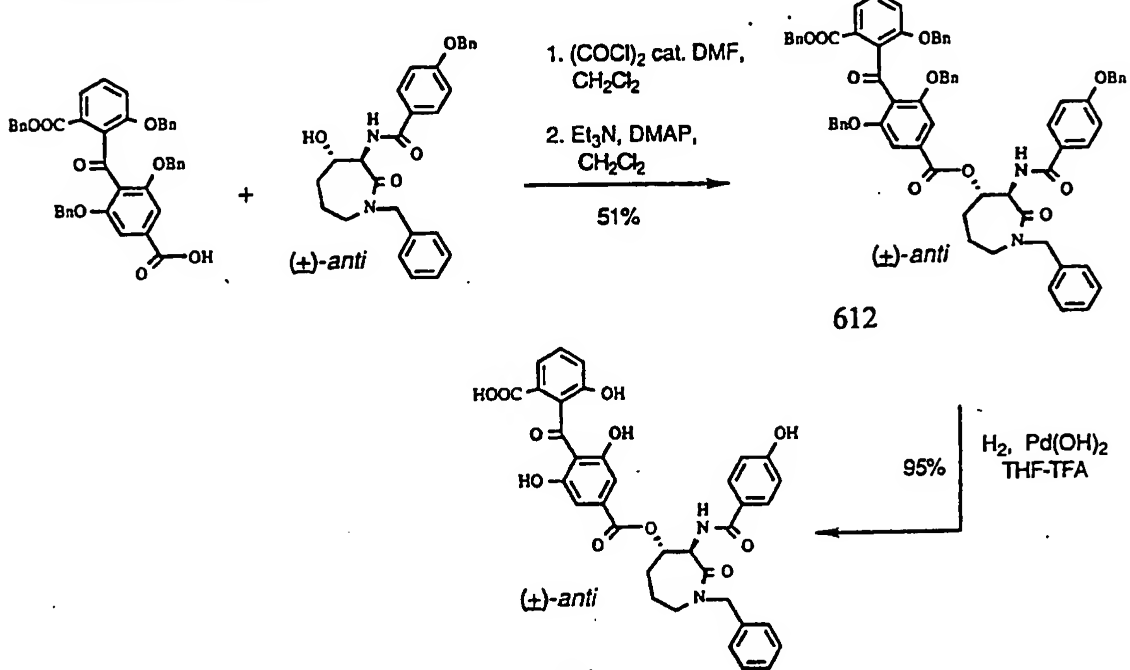


521

tert-butyl 4-(2,6-dibenzyloxybenzoyl)-3,5-dibenzyloxybenzoate (360 mg, 0.51 mmol) was placed in formic acid(10 ml). The resulting suspension was stirred for 20 min and intermittantly heated with a heat gun. The reaction was poured over water (300 ml) and stirred. The solids that precipitated were then filtered. Next, the solids were dissolved in ethyl acetate, and dried over sodium sulfate. The sodium sulfate was filtered off, and the filtrate was concentrated in vacuo and recrystalized in hexane: ethyl acetate to yield a light yellow solid (Acid 175 mg). This

material was dissolved in dimethylformamide (2 ml). Potassium carbonate (2.2 eq.) was then added. Next, benzyl bromide (5 eq) was added. The reaction was stirred at R.T. for 2 h. The reaction was taken up in ethyl acetate and 1N HCl, and placed in a separatory funnel. The organic layer was isolated, dried over sodium sulfate, concentrated in vacuo, and flash chromatographed eluting with hexane:ethyl acetate / 90:10. The major product was isolated as a white foam. This material was then dissolved in a solution of methanol:isopropyl alcohol:water / 45:45:10 with 5% potassium hydroxide. The solution was stirred for 4 h at R.T. The organic solvents were then removed in vacuo, and to the remaining aqueous solution was acidified with 1N HCl. Ethyl acetate (100 ml) was then added. The biphasic solution was then placed in a separatory funnel and the organic phase was isolated, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was recrystalized in hexane:ethyl acetate to yield a light yellow solid (92 mg). This benzophenone acid was then converted to Compound 521. Compound 521 was prepared through coupling and reduction in the same was as for Compound 547. A light yellow solid was obtained through reverse phase C-18 HPLC and subsequent lyophilization (7.5 mg). The structure was identified as Compound 521 through ^{1}H NMR.

(+)-*anti*-2-(4-Hydr xybenzamido)-3-[3,5-dihydroxy-4-(2-hydr xy-6-carboxyphenylcarbonyl)benzoyl xy]-N-benzylcaprolactam (COMPOUND 523)



612

523

COMPOUND 612

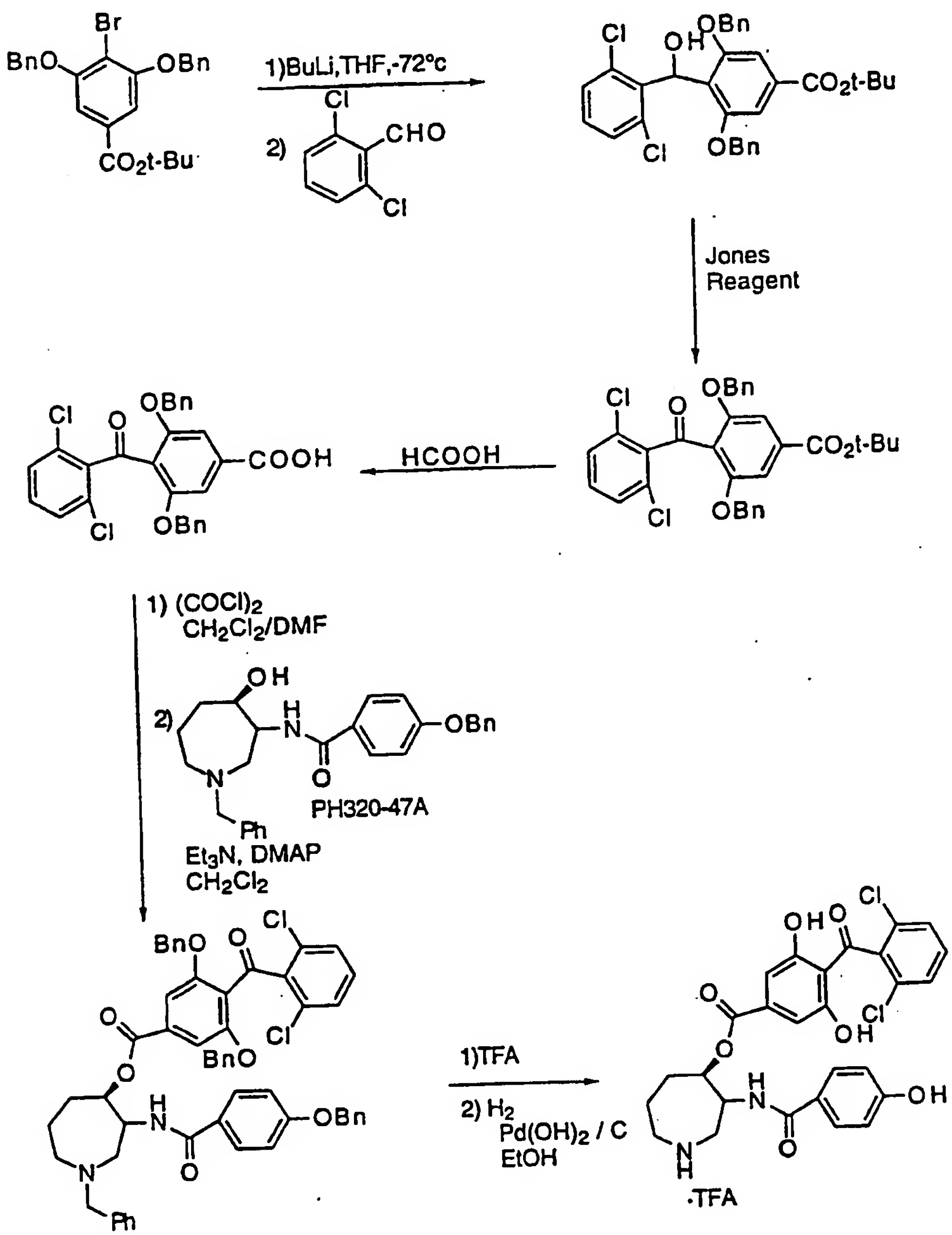
To a solution of 4-(2-benzyloxy-6-benzyloxycarbonyl)-3,5-dibenzyloxybenzoic acid (304.7 mg, 0.449 mmol) in CH_2Cl_2 (3ml) was added 2 drops of DMF and oxalyl chloride (2.0 M solution in CH_2Cl_2, 561 μL, 1.123 mmol) at room temperature. The mixture was kept stirring at room temperature for 1 hr. Solvents were removed and the acid chloride residue was taken into CH_2Cl_2 (5ml) after drying under vaccuum for 1 hr.

A solution of the lactam alcohol (200 mg, 0.449 mmol), Et_3N (227.19 mg, 312.9 μL, 2.245 mmol) and DMAP (10.97 mg, 0.089 mmol) in CH_2Cl_2 (5ml) was treated with the acid chloride-CH_2Cl_2 solution made above at 5°C. The reaction mixture was allowed to stir at room temperature for 3 hr and then chromatographed on silica gel eluting with 5:3 to 1:1 hexane:EtOAc. The product was obtained as white solid (250 mg, 51%).

COMPOUND 523

Compound 612 (225 mg, 0.204 mmol) was dissolved in THF (20 ml) and treated with a few drops of TFA and $Pd(OH)_2$ (70 mg, 30% by weight on carbon). The mixture was subject to hydrogenolysis with a H_2 balloon for 5 hr. THF was removed *in vacuo* and the residue taken into MeOH. The MeOH solution was concentrated after filtering through a pad of celite to give Compound 523 as a yellow solid (126 mg, 95%). m.p. 174-176 (dec)°C; 1H NMR (CD_3OD) δ 7.90 (d, J = 8.4Hz, 1H, NH), 7.42 (d, J = 8.7Hz, 2H, ArH), 7.26 (d, J = 7.7Hz, 1H, ArH), 7.14-7.12 (s, br, 5H, ArH), 7.04 (t, J = 8.1Hz and J = 7.7Hz, 1H, ArH), 6.78 (d, J = 8.1Hz, 1H, ArH), 6.65 (s, 2H, ArH), 6.57 (d, J = 8.6Hz, 2H, ArH), 5.22 (m, 1H, H-3). 4.92 (m, 1H, H-2), 4.52 (d, J = 14.5Hz, 1H, NCHPh), 4.42 (d, J = 14.5Hz, NCHPh), 3.59 (t, br, 1H, H-6), 3.22 (dd, br, 1H, H-6), 1.87 (m, 2H, H-5), 1.62 (m, 1H, H-4), and 1.32 (m, 1H, H-4); IR (KBr) cm^{-1} 3398, 1717, 1708, 1635, 1606, and 1543. Anal. Calcd. for $C_{25}H_{30}N_2O_{11}\cdot 1.25H_2O$: C, 61.67; H, 4.88; N, 4.12. Found: C, 61.78; H, 5.02; N, 3.92. LRFAB (M + 1) : 655.

4-R*-4-[(2,6-Dichlorobenzoyl)-3,5-dihydroxybenzoyl xy]-3-R*-(4-hydroxybenzamid)perhydr azepine triflu roacetic acid (COMPOUND 524)



608

524

1,1-Dimethylethyl-3,5-dibenzyloxy-4-(2,6-dichloromethylphenylhydroxy)benzoate

2.80 ml (7.03 mmole) of 2.5 M n-butyllithium was added dropwise to a cold solution (-72° C) of 3.00 g (6.39 mmole) of 1,1-dimethylethyl-4-bromo-3,5-dibenzyloxybenzoate in 40 ml of anhydrous tetrahydrofuran (THF) under nitrogen. The temperature of the solution was maintained below -70° C throughout the addition and the solution was stirred in the cold for ten minutes. A solution of 1.20 g (7.03 mmole) of 2,6-dichlorobenzaldehyde in 10 ml of THF was added dropwise to the solution maintaining the temperature below -65° c throughout the addition. The solution was allowed to warm to room temperature as it stirred for two hours. The solution was partitioned between 20 ml of 1N hydrochloric acid and 50 ml of ethyl acetate while stirring for five minutes. The organic layer was separated, washed with water, saturated brine and dried over magnesium sulfate. The solvent was evaporated and the residue was recrystallized from ethanol to yield 1.90 g (55%) of white crystals. Anal. Calcd for $C_{30}H_{30}Cl_2O_5$: C, 67.97; H, 5.35. Found: C, 67.99; H, 5.20

1,1-Dimethylethyl-4-(2,6-dichlorobenzoyl)-3,5-dibenzyloxybenzoate

To a cold solution (0° C) of 1,1-dimethylethyl-3,5-dibenzyloxy-4-(2,6-dichlorophenylmethylhydroxy)benzoate (1.00 g, 1.77 mmole) in 20 ml of acetone was added 5 ml of Jones reagent. As the Jones reagent was being added the solution became very thick. Therefore, an additional 20 ml of acetone was added. The reaction mixture was allowed to stir at room temperature for five hours. Isopropyl alcohol was added to the solution to destroy the Jones reagent. The reaction mixture was filtered through celite and washed with acetone. The solvent was removed in vacuo. The residue was taken up in 200 ml of ether. The ether solution was washed with saturated sodium bicarbonate, saturated brine and dried over magnesium sulfate. The solvent was evaporated to yield 0.79 g (79%) of a white solid.

4-(2,6-Dichlorobenzoyl)-3,5-dibenzyloxybenzoic acid

A solution of 0.95 g of the prime compound (1.70 mmole) in 20 ml of formic acid was stirred at room temperature for three hours. The solution was poured over ice water, collected and dried. Recrystallized from toluene to yield 0.75 g (87%) of yellow crystals.

Trans-N-Benzyl-4-[4-(2,6-dichlorobenzoyl)-3,5-dibenzyloxybenzoyloxy]-3-(4-benzyloxybenzamido)perhydroazepine (COMPOUND 608)

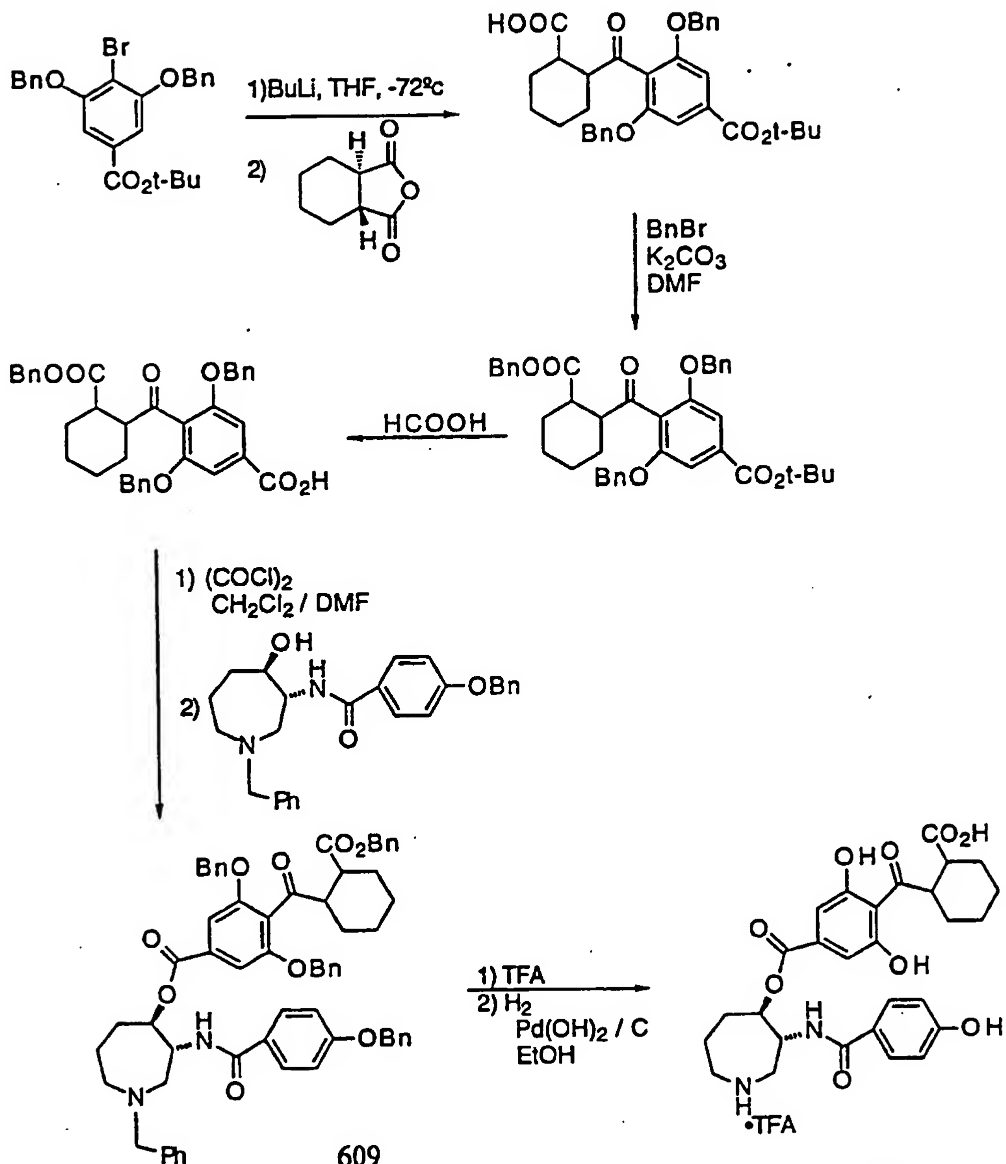
A solution of 0.40 g (0.79 mmole) of 4-(2,6-dichlorobenzoyl)-3,5-dibenzyloxybenzoic acid in 20 ml of methylene chloride containing a trace (approximately 1 μL) of dimethylformamide was cooled to 0°C. A 2.0 M solution of oxalyl chloride (0.45 ml, 0.89 mmole) was added and the solution was stirred under a nitrogen atmosphere at room temperature for two hours. The solvent was removed in vacuo. The residue was taken up twice in 20 ml portions of methylene chloride and the solvent was removed in vacuo. The residue was dissolved in 8 ml of methylene chloride and added dropwise to a solution of 0.38 g (0.89 mmole) of trans-N-benzyl-3-(4-benzyloxybenzamido)-4-hydroxyperhydroazepine, 0.06 ml (0.89 mmole) of triethylamine and 4.00 mg of DMAP in 10 ml of methylene chloride. The solution was stirred at room temperature under nitrogen for twenty-four hours. The solution was diluted with 30 ml of methylene chloride and washed with saturated sodium bicarbonate, saturated brine and dried over magnesium sulfate. The solvent was removed in vacuo The residue was chromatographed on silica gel eluting with hexane - ethyl acetate (70 : 30). Yield 0.30 g (41%) of a clear oil.

4-R*-4-[(2,6-dichlorobenzoyl)-3,5-dihydroxybenzoyloxy]-3-R*-(4-hydroxybenzamido)perhydroazepine trifluoroacetic acid (COMPOUND 524)

A solution of 3.00 g (0.33 mmole) of trans-N-benzyl-4-[4-(2,6-dichlorobenzoyl)-3,5-dibenzyloxybenzoyloxy)-3-(4-benzyloxybenzamido)perhydroazepine in 15 ml of ethanol was

treated with 0.05 ml (0.65 mmole) of trifluoroacetic acid. The solution was stirred at room temperature for five minutes. The solvent was removed in vacuo. The residue was treated twice with 15 ml portions of ethanol and evaporated to remove the excess trifluoroacetic acid. The residue was taken up in 15 ml of ethanol, cooled to 0° C, and 0.05 g of moist 10% palladium hydroxide on carbon was added. The mixture was then stirred under an atmosphere of hydrogen for sixteen hours at room temperature. The mixture was filtered, evaporated and the residue was chromatographed on a 41 X 250 mm C 18 column (solvent A: 95 : 5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile;gradient 0-50% B over 60 min., flow 25 ml / min.). The pure fractions were pooled to yield 22.7 mg (10%) of a yellow powder, of Compound 524, mp 179 - 183°C. IR (KBr): 3425, 2875, 1677, 1607, 1508, 1429, 1370, 1239, 1200, 777 cm^{-1}. Anal Calcd for $C_{27}H_{24}Cl_2N_2O_7 \cdot H_2O \cdot 1.4\ C_2HF_3O_2$: C, 48.56; H, 3.74; N, 3.80. Found: C, 48.57; H, 4.02; N, 3.46.

Trans-4-R*-[4-(2-trans-carb xycyclohexylcarb nyl)-3,5-dihydroxybenzyloxy]-3-R*-(4-hydroxybenzamido)p rhydroazepin trifluoroacetic acid salt (COMPOUND 525)



609

525

1,1-Dim thylethyl-3,5-dibenzyloxy-4-(2-trans-carboxycyclohexyl-carbonyl)b nzoate

2.8 ml (7.03 mmole) of 2.5 M n-butyllithium was added dropwise to a cold solution (-72 °C) of 3.0 g (6.39 mmole) of 1,1-dimethylethyl-4-bromo-3,5-dibenzyloxybenzoate in 40 ml of anhydrous tetrahydrofuran (THF) under nitrogen. The solution was stirred in the cold for ten minutes. A solution of 1.2 g (7.03 mmole) of trans-1,2-cyclohexanedicarboxylic anhydride in 10 ml of THF was added dropwise maintaining the temperature below -70 °C. The solution was stirred in the cold for two hours. The solution was poured into 150 ml of saturated ammonium chloride and 350 ml of ether. The reaction mixture was stirred for thirty minutes. The organic layer was separated, washed with 0.1 N hydrochloric acid, saturated brine and dried over magnesium sulfate. The solvent was evaporated to yield 3.4 g (98 %) of a clear oil.

1,1-Dimethylethyl-4-(4-(2-trans-benzyloxycarbonyl-cyclohexylcarbonyl))-3,5-dibenzyloxybenzoate

To a solution of 3.40 g (6.20 mmole) of 1,1-dimethylethyl-3,5-dibenzyloxy-4-(2-trans-carboxycyclohexyl-carbonyl)benzoate in 20 ml of dry DMF was added 0.90 g (6.20 mmole) of potassium carbonate and 0.70 ml (6.20 mmole) of benzyl bromide. The solution was stirred at room temperature under nitrogen for two hours. The solution was poured over 100 ml of ice water, extracted twice with 150 ml portions of ether. The ether solution was washed with water, saturated brine and dried over magnesium sulfate. The solvent was evaporated and the residue was chromatographed on silica gel eluting with 5 % - 10 % ethyl acetate - hexane to yield 1.0 g (25 %) of a clear oil.

4-(4-(2-trans-benzyloxycarbonylcyclohexylcarbonyl)-3,5-dibenzyloxybenzoic acid

A solution of 1.10 g (1.17 mmole) of 1,1-dimethylethyl-4-(4-(2-trans-benzyloxycarbonylcyclohexyl-carbonyl)-3,5-dibenzyloxybenzoate in 10 ml of formic acid was

stirred at room temperature for four hours. The solution was poured over ice water, collected and dried to yield 0.78 g (82.8%) of a white solid. Anal. Calcd for $C_{36}H_{34}O_7$: C, 73.63 ; H, 6.18. Found : C, 73.75 ; H,6.08.

Trans-N-benzyl-4-(4-(2-trans-benzyloxycarbonylcyclohexyl-carbonyl)-3-(4-benzyloxybenzamido)perhydroazepine (COMPOUND 609)

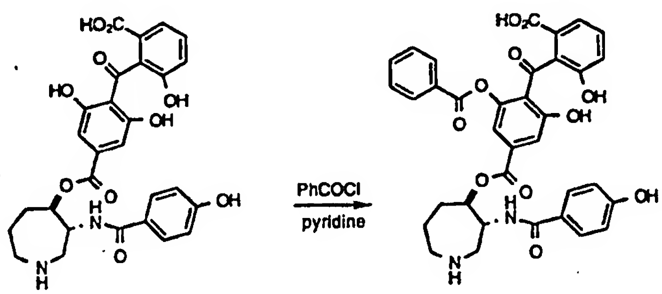
A solution of 0.40 g (0.69 mmole) of 4-(4-(2-trans-benzyloxycarbonylcyclohexylcarbonyl)-3,5-dibenzyloxybenzoic acid in 8 ml of methylene chloride containing a trace (amount approximately 1 µL) of dimethylformamide was cooled to 0°C. A 2.0 M solution of oxalyl chloride (0.59 ml, 1.18 mmole) was added and the solution was stirred under nitrogen for 2.5 hours. The reaction mixture was evaporated, and the residue was evaporated twice from 15 ml of methylene chloride. The residue was dissolved in 8 ml of methylene chloride and added to a solution of 0.34 g (0.78 mmole) of trans-N-benzyl-3-(4-benzyloxybenzamido)-4-hydroxyazepine, 0.08 ml (0.78 mmole) of triethylamine and 4.0 mg of DMAP in 10 ml of methylene chloride. The solution was stirred at room temperature under nitrogen for sixteen hours. The solution was diluted with 30 ml of methylene chloride and washed with saturated sodium bicarbonate, saturated brine and dried over magnesium sulfate. The solvent was evaporated and the residue was chromatographed on silica gel eluting with ethyl acetate - hexane (1 : 4). Yield of 0.39 g (57%) of a clear oil.

Trans-4-R*-(4-(2-trans-carboxycyclohexylcarbonyl)-3,5-dihydroxybenzyloxy)-3-R*-(4-hydroxybenzamido)perhydroazepine trifluoroacetic acid salt (COMPOUND 525)

A solution of 0.39 g (0.39 mmole) of trans-N-benzyl-4-(4-(2-trans-benzyloxycarbonylcyclohexylcarbonyl))-3-(4-benzyloxy-benzamido)perhydroazepine in a 20 ml solution of methanol, ethanol and methylene chloride (1:2:2) was treated with 0.06 ml (0.77 mmole) of trifluoroacetic acid for five minut s. The solvent was evaporated, and the methanol,

ethanol, methylene chloride solvent was added twice more and evaporated. The residue was taken up in 15 ml of ethanol, cooled to 0°C and 0.05 g of palladium hydroxide on carbon was added. The mixture was then stirred under an atmosphere on hydrogen for six hours at room temperature. The mixture was filtered, evaporated and the residue was chromatographed on a 41 X 250 mm C18 column (solvent A: 95 : 5 water / acetonitrile + 0.1% TFA; solvent B : 100% acetonitrile ; gradient 0 - 50% B over 60 min., flow 25 ml / min.). The pure fractions were pooled to yield 57 mg (21%) of Compound 525 as a yellow powder, mp 199 - 204 ° C. IR (KBr) : 1676, 1607, 1508, 1427, 1365, 1276, 1203, 757 cm^{-1}. Anal. Calcd for $C_{28}H_{32}N_2O_9 \circ H_2O \circ 1.2$ TFA : C, 52.50 ; H, 5.10 ; N, 4.02. Found : C, 52.83 ; H, 5.45 ; 3.97.

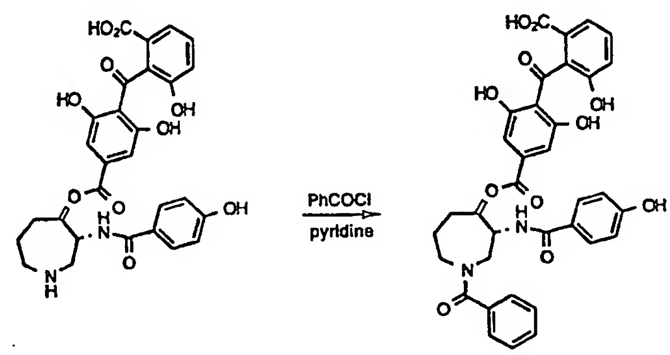
Trans-4-[4-(2-carboxy-6-hydroxybenzoyl)-3-b nzoyloxy-5-hydroxybenzoyloxy]-3-(4-hydroxybenzamido)perhydroazepine Trifluoroacetic Acid Salt (COMPOUND 528)



528

A solution of 9.1 mg (0.013 mmol) of (-)-trans-4-(4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy)-3-(4-hydroxybenzamido)perhydroazepine trifluoroacetic acid salt in 0.15 ml of dry pyridine was treated with 1.8 μL (2.2 mg, 0.016 mmol) of benzoyl chloride. The mixture was stirred for 24 h at room temperature, after which an additional 6.4 μL of benzoyl chloride was added. After an additional 24 h, 4 ml of benzoyl chloride was added, and the mixture was allowed to stand for a final period of 24 h, after which the reaction was quenched by the addition of 2 ml of methanol. The mixture was evaporated to a residue which was chromatographed on a 21 x 250 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0-50% B over 60 min, flow: 15 ml/min). The pure fractions were pooled and evaporated and then lyophilized from water to give 4.8 mg of Compound 528 as a white fluffy solid. FABMS: m/z 655 (M + H).

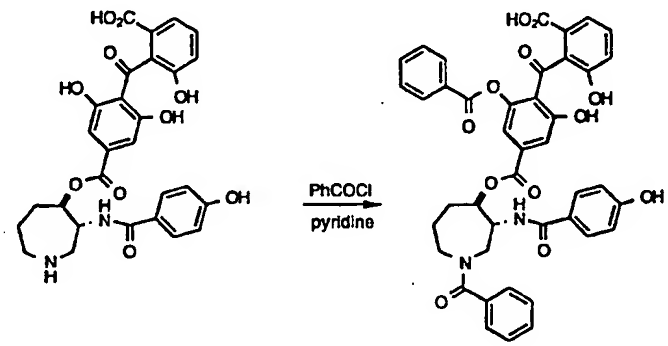
N-Benzoyl-trans-4-[4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)perhydroazepine (COMPOUND 529)



529

A solution of 9.1 mg (0.013 mmol) of (-)-trans-4-(4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy)-3-(4-hydroxybenzamido)perhydroazepine trifluoroacetic acid salt in 0.15 ml of dry pyridine was treated with 1.8 μL (2.2 mg, 0.016 mmol) of benzoyl chloride. The mixture was stirred for 24 h at room temperature, after which an additional 6.4 μL of benzoyl chloride was added. After an additional 24 h, 4 μL of benzoyl chloride was added, and the mixture was allowed to stand for a final period of 24 h, after which the reaction was quenched by the addition of 2 ml of methanol. The mixture was evaporated to a residue which was chromatographed on a 21 x 250 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0-50% B over 60 min, flow: 15 ml/min). The pure fractions were pooled and evaporated and then lyophilized from water to give 4.6 mg of Compound 529 as a white fluffy solid. FABMS: m/z 677 (M + Na), 655 (M + H).

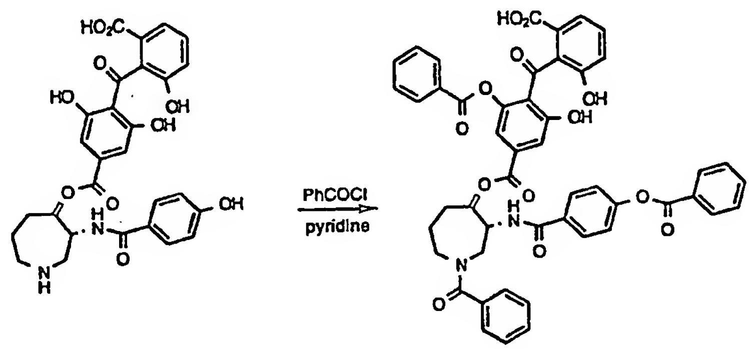
N-Benzoyl-trans-4-[4-(2-carboxy-6-hydroxybenzoyl)-3-benzoyloxy-5-hydroxybenzoyloxy]-3-(4-hydroxybenzamido)perhydroazepine (COMPOUND 530)



530

A solution of 9.1 mg (0.013 mmol) of (-)-trans-4-(4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy)-3-(4-hydroxybenzamido)perhydroazepine trifluoroacetic acid salt in 0.15 ml of dry pyridine was treated with 1.8 μL (2.2 mg, 0.016 mmol) of benzoyl chloride. The mixture was stirred for 24 h at room temperature, after which an additional 6.4 μL of benzoyl chloride was added. After an additional 24 h, 4 μL of benzoyl chloride was added, and the mixture was allowed to stand for a final period of 24 h, after which the reaction was quenched by the addition of 2 ml of methanol. The mixture was evaporated to a residue which was chromatographed on a 21 x 250 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0-50% B over 60 min, flow: 15 ml/min). The pure fractions were pooled and evaporated and then lyophilized from water to give 5.3 mg of Compound 530 as a white fluffy solid. FABMS: *m/z* 781 (M + Na), 759 (M + H).

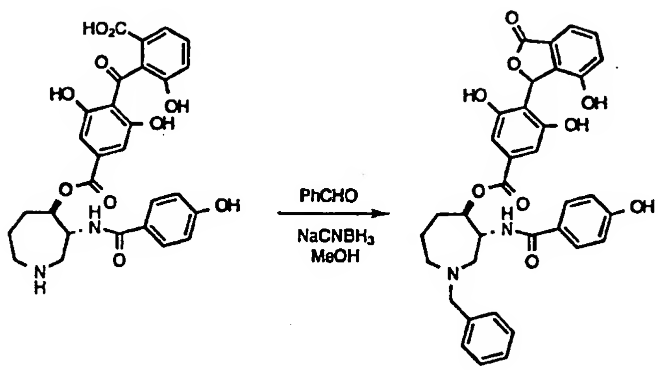
N-Benzoyl-trans-4-[4-(2-carboxy-6-hydroxybenzoyl)-3-benzoyloxy-5-hydroxybenz yloxy]-3-(4-benzoyloxybenzamido)perhydroazepin (COMPOUND 531)



531

A solution of 9.1 mg (0.013 mmol) of (-)-trans-4-(4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy)-3-(4-hydroxybenzamido)perhydroazepine trifluoroacetic acid salt in 0.15 ml of dry pyridine was treated with 1.8 μL (2.2 mg, 0.016 mmol) of benzoyl chloride. The mixture was stirred for 24 h at room temperature, after which an additional 6.4 μL of benzoyl chloride was added. After an additional 24 h, 4 μL of benzoyl chloride was added, and the mixture was allowed to stand for a final period of 24 h, after which the reaction was quenched by the addition of 2 ml of methanol. The mixture was evaporated to a residue which was chromatographed on a 21 x 250 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0-50% B over 60 min, flow: 15 ml/min). The pure fractions were pooled and evaporated and then lyophilized from water to give 2.9 mg of Compound 531 as a white fluffy solid. FABMS: *m/z* 885 (M + Na), 863 (M + H).

Trans-N-benzyl-4-[4-(3-hydroxyphthalido)-3,5-dihydroxybenzoyl-oxy]-3-(4-hydroxybenzamido)p rhydroaz pine Triflu roacetic Acid Salt Hydrate (COMPOUND 535)

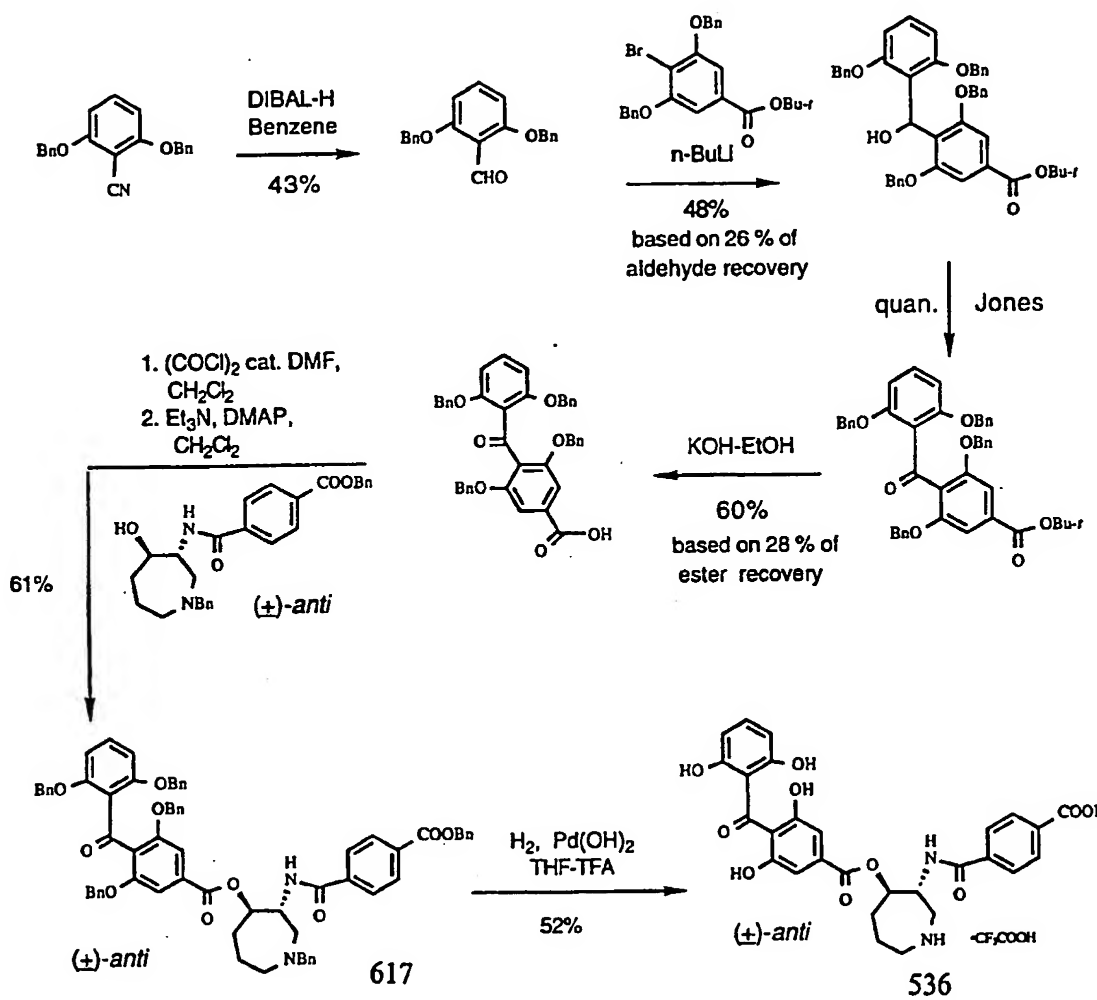


510 535

A solution of 15.6 mg (0.022 mmol) of (-)-trans-4-(4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy)-3-(4-hydroxybenzamido)perhydroazepine trifluoroacetic acid salt in 0.30 ml of methanol was treated with 4.4 µL (4.6 mg, 0.043 mmol) of benzaldehyde and 21.7 µl (0.022 mmol) of a 1 M solution af sodium cyanoborohydride in tetrahydrofuran. The mixture was stirred for 24 h at room temperature, after which the reaction was quenched by the addition of 0.30 ml of TFA. The mixture was stirred for 3 h and then evaporated to a residue which was chromatographed on a 21 x 250 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0-50% B over 60 min, flow: 15 ml/min). The pure fractions were pooled and evaporated and then

lyophilized from water to give 10.1 mg of the title compound as a white fluffy solid. FABMS: *m/z* 625 (M + H). Anal. Calcd for $C_{35}H_{32}N_2O_8 \cdot 3\ H_2O \cdot$ TFA: C, 56.06; H, 4.96; N, 3.53. Found: C, 55.76; H, 4.87; N, 3.82.

(±)-*anti*-3-(4-carboxybenzamido)-4-[3,5-dihydroxy-4-(2,6-dihydr xy)phenylcarb nyl]benzoyloxyhexahydroaz pin trifluoroacetic acid salt (COMPOUND 536)



The 2,6-dibenzyloxybenzonitrile (4.0 g, 12.68 mmol) was dissolved in benzene (30 ml) and cooled to 5°C. The DIBAL-H (1.0 M in Hexane, 15.2 ml, 15.2 mmol) was then added and the reaction was allowed to warm up to room temperature and stirred for 4 days. H_2O (2 ml) was slowly added to the reaction, followed by 2N HCl until pH was 3.0. Solids precipitated were filtered off and washed with H_2O and EtOAc.

The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was flash chromatographed on silica gel eluting with 6:1 Hexane:EtOAc to yield yellow oil (1.69 g, 43%), which was taken to the next, coupling reaction.

To a solution of t-butyl ester bromide (1.9 g, 4.08 mmol) in THF (40 ml), precooled to -75°C, was added n-BuLi (2.5M, 1.79 ml, 4.49 mmol). The resulting purple solution was allowed to stir at -75°C for 30 min, and a solution of aldehyde (1.3 g, 4.08 mmol) in THF (20 ml) was added in a period of 10 min. The mixture was allowed to warm up to -65°C in 20 min. The color of reaction changed from purple to yellow. The reaction mixture was poured into 0.5N HCl (50 ml) after warming up to 0°C, extracted with EtOAc (100 ml), and washed with brine. The crude material after concentration was purified on a silica gel column eluting with 8:1 Hexane:EtOAc to recover starting material aldehyde (0.5 g, 26%) and yield pure coupling product (1.0 g, 48%, based on 26% of recovered aldehyde).

The coupling product (1.0 g, 1.41 mmol) was dissolved in acetone (40 ml) and treated with Jones's reagent (ca. 2ml) at 5°C until the color of the reaction remained essentially the same color as the Jone's reagent. The reaction was then stirred at room temperature for 1hr. Acetone was removed *in vacuo* and residue was taken into EtOAc, washed with brine, dried over Na_2SO_4, and concentrated. The pure product was obtained as bright yellow foam from a short silica gel column eluting with 5:1/Hexane:EtOAc (997 mg, 100%).

The t-butyl ester of benzophenone (565mg, 0.779 mmol) was suspended in EtOH-H_2O (9:1, 10 ml) and treated with KOH (2N, 8 ml). The resulting cloudy mixture was warmed to 70°C for 4 hr. Ethanol was removed *in vacuo*. The aqueous residue was diluted with EtOAc and water, and acidified by 1N HCl. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography of the crude with 5:1 to 1:1 /Hexane:EtOAc afforded recovered starting material ester (160 mg, 28%) and yielded the corresponding acid as a yellow solid (220 mg, 60%, based on 28% of recovered ester).

COMPOUND 617

To a solution of benzophenone acid (200 mg, 0.307 mmol) in CH_2Cl_2 (3ml) was added cat. DMF and oxalyl chloride (2.0 M solution in CH_2Cl_2, 384 μL, 0.768 mmol) at room temperature The mixture was stirred at room temperature for 1 hr. Solvents were removed and the acid chloride residue was taken into CH_2Cl_2 (5ml) after drying over vacuum for 1hr.

A solution of azepine alcohol (SPC 104101, 140.8 mg, 0.307 mmol), Et_3N (31.1 mg, 43 μL, 0.307 mmol) and DMAP (7.5 mg, 0.06 mmol) in CH_2Cl_2 (5ml) was treated with the freshly made acid chloride-CH_2Cl_2 solution at 5°C. The reaction mixture was allowed to stir at r. t. for 3 hr and then chromatographed on silic gel eluting with 3:2 / hexane:EtOAc. The product was obtained as pale yellow foam-like solid (205 mg, 61%).

COMPOUND 536

The prior product (200 mg, 0.183 mmol) was dissolved in THF (20ml) and treated with few drops of TFA and 10% $Pd(OH)_2$ (120mg, 62 mol %). The mixture was subjected to hydrogenolysis at 50 psi for 30 hr. THF was removed *in vacuo* and the residue taken into MeOH. The MeOH solution was concentrated after filtering through a pad of celite and chromatographed on 41 x 300 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0-100% B over 60 min, flow: 25 ml/min). The pure fractions were evaporated to give two yellow solids. The minor product (15.0 mg) remained identified. The major product was found to be Compound 536 (63.5 mg, 52%). m.p. 176-178 (dec)°C; 1H nmr (CD3OD) δ 8.06 (d, J = 8.4Hz, 2H, ArH), 7.80 (d, J = 8.5Hz, 2H, ArH) 7.18 (t, J = 8.3 and 8.3 Hz, 1H, ArH), 6.94 (s, 2H, ArH), 6.26 (d, J = 8.3Hz, 2H, ArH), 5.42 (m, 1H, C_4-H), 4.54 (m, 1H, C_3-H), 3.50 (d, br, 2H, C_7-H or C_2-H), 2.30 and 2.09 (m and m, 1H and 3H, C_5-H and C_6-H); IR (KBr) cm^{-1} 3392, 1707, 1676, 1626, and 1593. Anal. Calc. for $C_{28}H_{26}N_2O_{10}\cdot3.0H_2O\cdot1.0TFA$: C, 50.14; H, 4.63; N, 3.90. Found: C, 50.26; H, 4.33; N, 4.21. LRFAB (M + 1) : 551.

anti-4-[4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-hexahydro-3-(indole-5-carboxamido)azepine, trifluoroacetic acid salt (COMPOUND 538)

anti-hexahydro-4-hydroxy-3-(indole-5-carboxamido)-1-phenylmethylazepine

A cooled (5°C) solution of lithium aluminum hydride/tetrahydrofuran (Aldrich, 1.0N, 6 ml, 6 mmol) under nitrogen was treated with *anti*-3-aminohexahydro-4-hydroxy-1-phenylmethylazepin-2-one (0.47g, 2.0 mmol) at a rate to keep the pot temperature below 10°C. The mixture was stirred for 16h at room temperature, for 2h at reflux, then cooled on an ice bath. The reaction mixture was treated sequentially dropwise with water (0.23 ml), 15% sodium hydroxide (0.23 ml), and water (0.70 ml), and filtered. The filter cake was rinsed with tetrahydrofuran and the filtrate was concentrated *in vacuo* to afford the crude perhydroazepine. Meanwhile, a solution of indole-5-carboxylic acid (0.45 g, 2.8 mmol) in anhydrous tetrahydrofuran (8 ml) under nitrogen was treated with 1,1'-carbonyldiimidazole (0.46 g, 2.8 mmol); some bubbling ensued, which subsided after a few minutes. The solution was stirred for 1.5 h, then combined with the crude perhydroazepine. The mixture was stirred at room temperature for 40 h and concentrated *in vacuo*. The residue was dissolved in methanol (8 ml) and treated with potassium hydroxide (1.0 g) in water (2.0 ml). The solution was stirred at room temperature for 2h, partially concentrated *in vacuo*, and diluted with water (10 ml). The aqueous suspension was extracted with methylene chloride (3 x 25 ml) containing some 2-propanol, and the combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo*, and chromatographed on silica gel (eluted with ethyl acetate) to afford *anti*-hexahydro-4-hydroxy-3-(indole-5-carboxamido)-1-phenylmethylazepine (0.47 g, 65%) as a white solid.

***anti*-4-[4-(2-carboph nylmeth xy-6-phenylmethoxybenzoyl)-3,5-bis-(ph nylmethoxy)benzoyloxy]hexahydro-3-(ind le-5-carboxamido)-1-phenylmethylazepine (COMPOUND 619)**

A solution of 4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)-3,5-bis-(phenylmethoxy)benzoic acid (0.24g, 0.35 mmol) in anhydrous methylene chloride (1.2 ml) was treated with N,N-dimethylformamide (2 drops), then with 2.0 N oxalyl chloride/methylene chloride (0.25 ml, 0.50 mmol), and stirred for one hour under nitrogen. The solution was concentrated *in vacuo*, placed under high vacuum for one hour, and dissolved in anhydrous methylene chloride (1.5 ml). *Anti*-hexahydro-4-hydroxy-3-(indole-5-carboxamido)-1-phenylmethylazepine (0.145g, 0.40 mmol) was suspended in anhydrous methylene chloride (1.0 ml), then treated with 4-dimethylaminopyridine (10mg), triethylamine (0.10 ml, 0.72 mmol), and the acid chloride solution prepared above. The mixture was stirred under nitrogen for 17h and concentrated *in vacuo*. Silica gel chromatography (eluted with 3% acetone/methylene chloride, then 5% acetone/methylene chloride) afforded *anti*-4-[4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)-3,5-bis(phenylmethoxy)benzoyloxy]hexahydro-3-(indole-5-carboxamido)-1-phenylmethylazepine (0.18g, 50%) as a colorless foam.

***anti*-4-[4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-hexahydro-3-(indole-5-carboxamido)azepine, trifluoroacetic acid salt (COMPOUND 538)**

A solution/suspension of *anti*-4-[4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)-3,5-bis(phenylmethoxy)benzoyloxy]hexahydro-3-(indole-5-carboxamido)-1-phenylmethylazepine (0.13g, 0.127 mmol) in reagent ethanol (5ml) in a 25 ml 2-neck flask under nitrogen was treated with trifluoroacetic acid (30 mg, 0.26 mmol) and with ethyl acetate (0.20 ml, for solubility), then with 20% $Pd(OH)_2/C$ (Pearlman's catalyst, 50mg). The flask was fitted with a baloon valve connected to a baloon containing hydrogen,

then purged with hydrogen and placed under positive hydrogen pressure for 20h. The flask was carefully purged with nitrogen and the solution filtered through celite (wash filter cake with ethanol), then the filtrate was concentrated *in vacuo*. The residue was taken up in methanol (15 ml) and trifluoroacetic acid (0.5 ml), gravity filtered, and the filtrate was diluted with de-ionized water (75 ml). The mixture was partially concentrated *in vacuo*, and the aqueous solution was freeze-dried for 18h. Collection of the yellow solid Compound 538, *anti*-4-[4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]hexahydro-3-(indole-5-carboxamido)-azepine, trifluoroacetic acid salt (71mg, 68%); mp 170-180°C. IR (KBr) 1680, 1635, 1607 cm^{-1}; mass spectrum (FAB): m/z 574; ^1H NMR (d_6-DMSO) δ 11.67 (s, 2H), 11.37 (s, 1H), 9.87 (s, 1H), 9.00 - 9.20 (m, 2H), 8.64 (d, 1H, J = 8 Hz), 8.06 (s, 1H), 7.56 (d, 1H, J = 8 Hz), 7.43 (s, 1H), 7.30 - 7.45 (m, 2H), 7.27 (t, 1H, J = 8 Hz), 7.05 (d, 1H, J = 8 Hz), 6.80 (s, 2H), 6.52 (br s, 1H), 5.30 (m, 1H), 4.55 (m, 1H), 3.25 - 3.50 (m, 2H), 3.10 - 3.25 (m, 2H), 2.05 - 2.20 (m, 1H), 1.80 - 2.05 (m, 3H). Anal. Calcd. for $C_{30}H_{27}N_3O_9 \cdot 1.9(C_2HO_2F_3) \cdot 2.0(H_2O)$: C, 49.14; H, 4.01; N, 5.09. Found: C, 49.10; H, 4.38; N, 4.88.

***anti*-4-[4-(2-carboxy-6-hydr xybenzoyl)-3,5-dihydroxybenzoyl-N-methylamino]hexahydro-3-(4-hydroxyb nzoylamino)azepine, trifluoroacetic acid salt (COMPOUND 539)**

Anti-hexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethyl-4-trifluoroacetylaminoazepine

A solution of hexahydro-3-(4-phenylmethoxy)-benzoylamino-1-phenylmethyl-azepin-4-one (0.87 g, 2.03 mmol) in ethanol (12 ml) was treated with hydroxylamine hydrochloride (0.19 g, 2.73 mmol), followed by 25% methanolic sodium methoxide (Aldrich, 0.20 g, 0.93 mmol), and was heated to 50°C for one hour. The mixture was cooled to room temperature and treated with additional 25% methanolic sodium methoxide (0.42 g, 1.94 mmol), then concentrated *in vacuo* to afford hexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepin-4-one oxime (0.89 g, 99%) as a colorless foam. A solution of this oxime (1.065 g, 2.4 mmol) in reagent ethanol (45 ml) in a Parr bottle was treated with Raney Nickel (Aldrich, one tsp.) and subjected to hydrogenation in a Parr apparatus at 47 - 51 psi for 5h. The bottle was carefully evacuated of hydrogen and the contents filtered through celite (washed with ethanol under nitrogen). The filtrate was gently concentrated *in vacuo* at 45°C, diluted with toluene, and further concentrated at ~45°C to remove the remaining ethanol. Meanwhile, a solution of trifluoroacetic acid (0.33 g, 2.9 mmol) in anhydrous tetrahydrofuran (6 ml) under nitrogen was treated with 1,1'-carbonyl diimidazole (0.50 g, 3.1 mmol). Some bubbling ensued, and the mixture was stirred for two hours, cooled on an ice bath, and combined under nitrogen with the residual amine prepared above (an additional 2 ml of tetrahydrofuran was used to rinse the CDI adduct into the reaction vessel). The mixture was stirred at room temperature for 18h and concentrated *in vacuo*, then the residue was chromatographed on silica gel (eluted with 3% acetone/methylene chloride, then with 8% acetone/methylene chloride) to afford, initially, *syn*-hexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethyl-4-trifluoroacetylaminoazepine (0.27 g) followed by *anti*-

hexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethyl-4-trifluoroacetylaminoazepine (0.40 g). The total yield of trifluoroacetamides was 0.67 g (53%); the *anti*-isomer could be recrystallized from acetonitrile.

anti-hexahydro-4-(methylamino)-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine

An ice-cooled (5°C) solution of *anti*-hexahydro-3-(4-phenylmethoxy)benzoyl-amino-1-phenylmethyl-4-trifluoroacetylaminoazepine (0.20 g, 0.38 mmol) in anhydrous N,N-dimethylformamide (2 ml) under nitrogen was treated dropwise with 1.0 N potassium *t*-butoxide/tetrahydrofuran (Aldrich, 0.40 ml, 0.40 mmol), then stirred for 20 min at room temperature and recooled (5°C). Dimethyl sulfate (38 μL, 0.40 mmol) was added *via syringe*, and stirring was continued at 5°C for 3h. The solution was added to a rapidly stirred mixture of methylene chloride (10 ml) and saturated sodium bicarbonate (5 ml) and the organic layer was separated. The aqueous layer was extracted with methylene chloride (10 ml) and the combined organic solution was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed on silica gel (eluted successively with 2%, 3%, and 4% acetone/methylene chloride) to afford the methylated intermediate (0.15 g) as a viscous colorless oil. This was dissolved in reagent methanol (1.5 ml), treated with a solution of potassium hydroxide (0.25 g, 4.5 mmol) in water (0.25 ml), and stirred at room temperature for 2.5h. The solution was partially concentrated to remove most of the methanol, diluted with water (5 ml), and extracted with methylene chloride (2x15 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford *anti*-hexahydro-4-(methylamino)-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.105 g, 62%) as a colorless oil.

***anti*-4-[3,5-Bis(phenylmeth xy)-4-(2-carb phenylmethoxy-6-phenylmethoxybenzoyl)b nzoyl-N-methylamino]hexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (COMPOUND 620)**

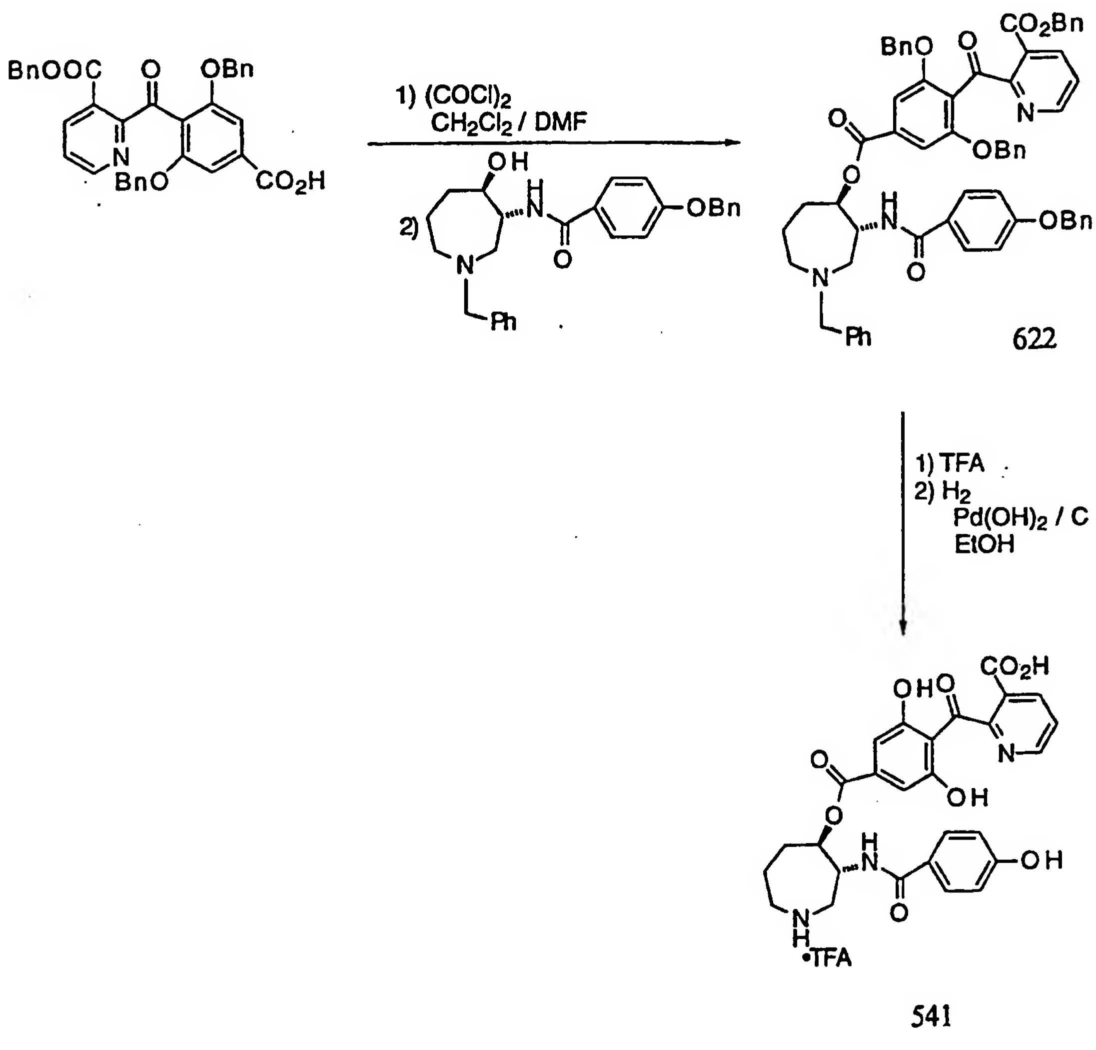
A solution of 3,5-bis(phenylmethoxy)-4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)benzoic acid (0.204 g, 0.30 mmol) in anhydrous methylene chloride (1.0 ml) was treated with N,N-dimethylformamide (2 drops), then with 2.0 N oxalyl chloride/methylene chloride (Aldrich, 0.22 ml, 0.44 mmol) and stirred for one hour under nitrogen. The solution was concentrated *in vacuo*, placed under high vacuum for 45 min, then dissolved in methylene chloride (2 ml) and combined with *anti*-hexahydro-4-(methylamino)-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.10 g, 0.225 mmol). The mixture was treated with 1.0 N sodium hydroxide (1.0 ml) and stirred for two hours, then diluted with methylene chloride (15 ml) and water (5 ml). The organic layer was separated and the aqueous solution was extracted with methylene chloride (2x15 ml). The combined organic solution was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed on silica gel (eluted successively with 5%, then 10% acetone/methylene chloride, then with 3% methanol/methylene chloride) to afford *anti*-4-[3,5-bis(phenylmethoxy)-4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)benzoyl-N-methylamino]hexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethyl-azepine (0.22 g, 88%) as a viscous colorless oil.

***anti*-4-[4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyl-N-methylamino]hexahydro-3-(4-hydroxybenzoylamino)azepine, trifluoroacetic acid salt (COMPOUND 539)**

A solution/suspension of *anti*-4-[3,5-bis(phenylmethoxy)-4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)benzoyl-N-methylamino]hexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.22 g, 0.20 mmol) in reagent ethanol (9 ml) in a 25 ml 2-neck round bottom flask was treated with trifluoroacetic acid (50 mg, 0.43 mmol), then with ethyl acetate (1 ml, for solubility). Pearlman's

catalyst (20% $Pd(OH)_2/C$, 90 mg) was added, then the flask was quickly purged with nitrogen and fitted with a baloon valve and baloon containing hydrogen. The mixture was purged with hydrogen and kept under positive hydrogen pressure for 20h. The flask was carefully evacuated of hydrogen and purged for several minutes with nitrogen. The solution was filtered through celite (wash filter cake with ethanol) and the filtrate was concentrated *in vacuo* and dissolved in N,N-dimethylformamide (1 ml). The solution was loaded onto a 41x250 mm C18 HPLC column and eluted as follows: A-0.1% TFA/95:5 water:acetonitrile, B-acetonitrile, 100% A to 50:50 A:B over 60 min collected at 25 ml/min. The appropriate fractions were combined and partially concentrated *in vacuo*, then freeze-dried overnight to afford *anti*-4-[4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyl-N-methylamino]-hexahydro-3-(4-hydroxybenzoylamino)azepine, trifluoroacetic acid salt (101 mg, 68%) as a voluminous pale yellow solid; mp 285-295°C (dec). R_f(6:1:1 n-BuOH/AcOH/H2O) 0.45; IR (KBr): 1682, 1633, 1620 cm^{-1}; ^1H NMR (d_6-DMSO) δ 11.68 (br s, 2H), 10.07 (br s, 1H), 9.92 + 9.85[1](s, 1H), 8.95 + 8.75[1] (br s, 2H), 8.28 + 8.181(d, 1H, J = 9 Hz), 7.67 + 7.581(d, 2H, J = 9 Hz), 7.20 - 7.40 (m, 2H), 7.00 - 7.10 (m, 1H), 6.78 - 6.85 (m, 2H), 6.00 (s, 2H), 4.40 - 4.80 (m, 2H), 3.00 - 3.40 (m, 4H), 2.85 + 2.771(s, 3H), 1.80 - 2.10 (m, 4H); mass spectrum(FAB): m/z 564. Anal. Calcd. for $C_{29}H_{29}N_3O_8 \cdot 1.1(C_2HO_2F_3) \cdot 3.0(H_2O)$: C, 50.43; H, 4.90; N, 5.66. Found: C, 50.32; H, 4.74; N, 5.74.

4-R*-4-[(((3-hydroxycarbonyl)-2-pyridinyl)carbonyl)-3,5-dihydroxybenzoyloxy]-3-R*-(4-hydroxybenzamido)perhydroazepine trifluoroacetic acid salt (COMPOUND 541)



Trans-N-benzyl-4-[(((3-benzyloxycarbonyl)-2-pyridinyl)carbonyl)-3,5-dibenzyloxybenzoyloxy]-3-(4-benzyloxybenzamido)perhydroazepine (COMPOUND 622)

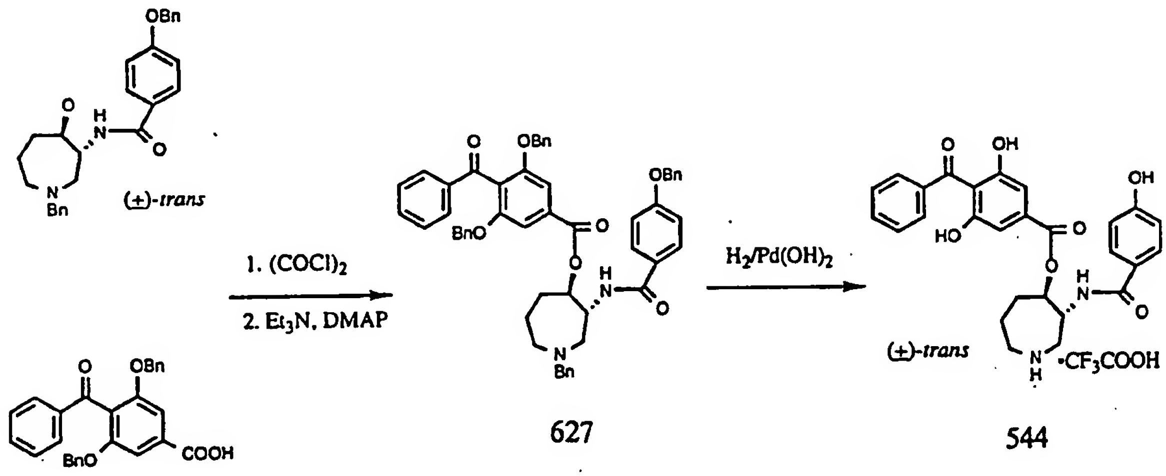
Carbonyldiimidizole (0.11 g, 0.65 mmole) was added to a solution of 4-[((3-benzyloxycarbonyl)-2-pyridinyl)carbonyl]-3,5-dibenzyloxybenzoic acid (0.25 g, 0.44 mmole) in 5 ml of

methylene chloride and the solution was stirred at room temperature for sixty minutes under nitrogen. The solution was added to a solution of 0.19 g (0.44 mmole) of trans-N-benzyl-3-(4-benzyloxybenzamido)-4-hydroxyperhydroazepine, 0.12 ml triethylamine, and 5 mg DMAP in 8 ml of methylene chloride. The solution was stirred at room temperature for twenty hours. The solution was diluted with 30 ml of methylene chloride, washed with water, saturated brine and dried over magnesium sulfate. The solvent was removed in vacuo. The residue was chromatographed on silica gel eluting with a gradient of 5% - 10% - 20% ethyl acetate - hexane to yield 70 mg of a clear oil.

4-R*-4-[((3-hydroxycarbonyl)-2-pyridinyl)carbonyl)-3,5-dihydroxybenzoyloxy]-3-R*-(4-hydroxybenzamido)perhydroazepine trifluoroacetic acid

A solution of 0.070 g (0.071 mmole) of trans-N-benzyl-4-[(((3-benzyloxycarbonyl)-2-pyridinyl)carbonyl)-3,5-dibenzyloxybenzoyloxy]-3-(4-benzyloxybenzamido)perhydroazepine in 8 ml of ethanol/methylene chloride (1:1) was treated with 10 μL (0.142 mmole) of trifluoroacetic acid. The solution was stirred at room temperature for fifteen minutes. The solvent was evaporated and the ethanol/methylene chloride solvent was added twice more and evaporated in order to remove the excess trifluoroacetic acid. The residue was taken up in 10 ml of absolute ethanol and cooled to 0 °C under nitrogen, and 0.030 g (0.025 mmole) of palladium hydroxide on carbon was added. The reaction mixture was stirred under an atmosphere of hydrogen for twenty-four hours. The reaction mixture was filtered, evaporated and the residue was chromatographed on a 21 X 250 mm C18 column (solvent A: 95 : 5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0 - 50% B over 60 min., flow 15 ml/min). The pure fractions were pooled and evaporated to yield 0.010 g of a yellow powder, mp 198-205° C. Anal. Calcd for $C_{27}H_{25}N_3O_9 \cdot 2H_2O \cdot 1.8TFA$: C, 47.32; H, 4.00; N, 5.41. Found: C, 47.27; H, 3.86, N, 5.47.

(+)-Trans-3-(4-Hydroxy)b nzamido-4-[(3,5-dihydr xy)-4-phenylcarb nyl]benzoyloxyperhydroazepin triflu r acetic acid salt (COMPOUND 544)



COMPOUND 627

To a mixture of N-benzylated azepine intermediate (0.3 g, 0.697 mmol), Et_3N (352.6 mg, 487 µl, 3.485 mmol), and DMAP (17.0 mg, 0.139 mmol) in CH_2Cl_2 (5 ml) was added a freshly made solution of benzophenone acid chloride (corresponding benzophenone acid: 336 mg, 0.766 mmol; oxalyl chloride: 2.0 M solution in CH_2Cl_2, 0.697 ml, 1.394 mmol and cat. DMF) in CH_2Cl_2 (5 ml) at room temperature. The reaction mixture was stirred at room temperature overnight. Flash chromatography of the reaction mixture on silica gel using 3:2/Hexane:EtOAc as an eluent gave white solid product (469 mg, 71%).

COMPOUND 544

The preceeding compound (300 mg, 0.315 mmol) in EtOAc:MeOH (1:1, 25 ml) was treated with CF_3COOH (37.76 mg,

25.5 μl, 0.33 mmol) and 20% $Pd(OH)_2$ on activated carbon (150 mg, 50% on weight basis). The mixture was subjected to hydrogenolysis at 45 psi for 15 hr. The crude product after filtration and concentration was taken into DMF (0.5 ml) and purified on C_{18}-HPLC column eluting with 5%-50% acetonitrile in H_2O containing 0.1% CF_3COOH. The title compound was obtained as white powder (118 mg, 62%). m.p. 204-206 (dec)°C; ^{1}HNMR (DMSO-d6) δ 8.42 (d, 1H, NHCO), 7.58 (d, J = 7.5 Hz, 2H, ArH), 7.28-7.15 (m, 4H, ArH), 6.82 and 6.80 (s and s, 2H, ArH), 6.72 (d, J = 8.1 Hz, 2H, ArH), 5.18 (s, br, 1H, CH-4), 4.45 (s, br, 1H, CH-3), 3.30 and 3.10 (s and s, br, 4H, CH_2N-2,7), 2.10-1.70 (m, 4H, CH_2-5,6); IR (KBr) cm^{-1} 3429, 1717, 1703, 1637, 1608, and 1509. Anal. Calcd. for $C_{27}H_{26}N_2O_7$ - 1.5 H_2O - 1.0 TFA: C, 55.15; H, 4.79; N, 4.44. Found: C, 54.97; H, 5.08; N, 4.06.

Trans-2-(4-Benzoyl-3,5-dihydroxybenz yl xy)-1-(4-hydroxybenzamido)cyclohexane (COMPOUND 545)

Trans-2-(4-benzoyl-3,5-dibenzyloxybenzoyloxy)-1-(4-benzyloxybenzamido)-cyclohexane (172 mg, 231 μmol) was dissolved in ethyl acetate (5 ml) and added to a stirring mixture of Pearlman's catalyst ($Pd(OH)_2$, 17 mg) in ethyl acetate (3 ml). The flask was evacuated under house vacuum and filled with $H_2(g)$ via balloon. After 3 h, additional Pearlman's catalyst (17 mg in 2 ml of EtOH) was added and left to stir overnight. TLC showed complete reaction (Starting material Rf=0.90, product Rf=0.41 in 50% EtOAc/hexanes.) The reaction mixture was filtered through Celite and concentrated to give the product as a yellow glass. The glass was triturated with water to give a pale yellow powder (122 mg, 86%): ^{1}H-NMR (DMSO, 300 MHz) δ 1.27-1.57 (4H, m), 1.63-1.77 (2H, s), 1.84-1.89 (1H, m), 2.05-2.17 (1H, m), 4.05-4.18 (1H, m), 4.91-5.01 (1H, m), 6.75 (2H, d, J = 8 Hz), 6.97 (2H, s), 7.24-7.36 (2H, m), 7.48 (3H, t), 7.69 (2H, d, J = 8 Hz), 8.10 (1h, d, J = 9 Hz), 9.85 (1H, s), 9.95 (2H, s): ^{13}C NMR (DMSO, 300 MHz) δ 24.14, 24.52, 24.57, 31.20, 31.79, 51.73, 75.70, 107.68, 108.19, 114.98, 125.96, 126.29, 126.35, 128.35, 129.11, 129.15, 129.45, 132.08, 133.80, 137.24, 155.75, 160.29, 165.47, 166.13, 194.87. IR (KBr) cm^{-1} 3360, 3271, 2943, 2858, 2360, 1708, 1659, 1610, 1541, 1507, 1450, 1424, 1369, 1347, 1278, 1240, 1177, 1106, 1047, 1011, 847, 771, 595. Anal. Calcd. for $C_{27}H_{25}NO_7$ - H_2O: C, 65.71; H, 5.51; N, 2.84. Found: C, 66.16; H, 5.49; N, 2.76.

Anti-3-(4-benzyloxybenzamido)-4-[3,5-dibenzyloxy-4-(3,4-dibenzyloxyphenylcarbonyl)benzoyloxy]-N-benzylperhydroazepine (COMPOUND 546)

3,5-Dibenzyloxy-4-[(3,4-dibenzyloxy)benzoyl]benzoic acid (500 mg, 0.768 mmol) was dissolved in anhydrous dichloromethane (6 ml). Anhydrous dimethylformamide (0.10 ml) was then added to the solution followed by oxalyl chloride (2 N in dichloromethane, 0.50 ml, 0.99 mmol). This solution was stirred for 1 h and then concentrated in vacuo. The resulting yellow oil was placed under high vacuum for a period of 1 h to make sure all of the excess oxalyl chloride was removed. The residue was dissolved in anhydrous dichloromethane (5 ml), and a solution of dimethylaminopyridine (67 mg, 0.550 mmol), triethylamine, and anti-N-benzyl-3-(4-benzyloxybenzamido)-4-hydroxyazepine (SPC-103853, 215 mg, 0.500 mmol) in anhydrous dichloromethane (5 ml) was added under nitrogen. The reaction was stirred at room temperature for 1.5 h. At this point dichloromethane (100 ml) and sodium hydroxide (0.5 N in water, 30 ml) were added to the reaction. The aqueous and organic layers were separated and the organic phase was washed with brine (100 ml). The organic phase was isolated and dried with magnesium sulfate. The magnesium sulfate was filtered off, and the solution was concentrated in vacuo to yield a yellow solid. The yellow solid was flash chromatographed on silica gel eluting with hexanes:ethyl acetate/9:1, 4:1, and 1:1 to yield a white solid of the title compound (400 mg, 75%): mp 65°C; ^1H NMR ($CDCl_3$) δ 1.80 (m, 2H, CH_2), 2.04 (m, 2H, CH_2), 2.73 (m, 2H, NCH_2), 3.01 (m, 2H, NCH_2), 3.59 (d, J = 12.5 Hz, 1H, NCH_2Ph), 3.80 (d, J = 12.9 Hz, 1H, NCH_2Ph), 4.32 (m, 1H, CH), 5.03 (s, 4H, CH_2Ph), 5.12 (s, 2H, CH_2Ph), 5.13 (s, 2H, CH_2Ph), 5.22 (m, 1H, CH), 5.24 (s, 2H, CH_2Ph), 6.74 (d, J = 7.8 Hz, 1H, NH), 6.86-7.56 (m, 39H, ArH); IR (KBr) cm^{-1} 1580 (COO-), 1654 (CO). Analysis calculated for $C_{69}H_{62}N_2O_8$: C, 77.95; H, 5.88; N, 2.63. Found: C, 77.70; H, 5.99; N, 2.60.

Anti-4-[3,5-dihydroxy-4-(3,4-dihydroxyphenylcarbonyl)] b nz yloxy-3-(4-hydroxyb nzamido)p rhydroazepine (COMPOUND 547)

Anti-3-(4-benzyloxybenzamido)-4-[3,5-benzyloxy-4-(3,4-dibenzyloxyphenylcarbonyl)benzoyloxy]-N-benzylazepine (240 mg, 0.23 mmol) and acetic acid were dissolved in methanol:ethyl acetate/2:1 in a 500 ml Parr bottle. Next, 5% palladium on activated carbon (45 mg) was added under nitrogen. The reaction mixture was placed on a Parr hydrogenator for 3 h. The mixture was then filtered over celite, and the filtrate was concentrated in vacuo to yield a yellow solid. The solid was flash chromatographed on silica gel eluting with dichloromethane:methanol/8:2 to yield a yellow solid of the title compound (57 mg, 48%): mp 176°C; ^{1}H NMR (D6 DMSO) δ 1.65 (m, 1H, CH_2), 1.78 (m, 1H, CH_2), 1.90 (2, 2H, CH_2), 2.85 (m, 4H, $N(CH_2)_2$), 4.20 (m, 1H, CH), 5.18 (m, 1H, CH), 6.70-7.70 (m, 9H, ArH), 8.16 (d, J = 8.4 Hz, 1H, NH); IR (KBr) cm^{-1} 1607 (CO), 1704 (COO-), 3431 (OH). Anal. calcd. for $C_{27}H_{26}N_2O_9 \cdot H_2O$: C, 59.50; H, 5.27; N, 5.14. Found: C, 59.54; H, 5.33; N, 4.93.

Trans-3-[3,5-Dihydroxy-4-(2-hydroxy)phenylcarbonyl]benzamido-4-(4-hydroxy)benz yloxyperhydroazepine (COMPOUND 548)

To a solution of trans-N-benzyl-3-[3,5-dibenzyloxy-4-(2-benzyloxy)phenylcarbonyl]benzamido-4-(4-benzyloxy)-benzoyloxyazepine (65 mg, 0.068 mmol) in EtOAc/MeOH (5/15 ml) was introduced $Pd(OH)_2$ on carbon (35 mg of 20% Pearlman's catalyst). The reaction mixture was subjected to hydrogenolysis at 45 psi for 24 h at room temperature. The catalyst was filtered off through a pad of celite and washed with MeOH. The combined filtrate was concentrated to dryness and purified by flash column chromatography (SiO_2: 60 ml, eluted with 10% to 20% MeOH in CH_2Cl_2). The title compound was obtained as a yellow solid (17 mg, 50%); mp 172-175°C, ^1H NMR (CD_3OD) δ: 7.65 (d, J = 8.7 Hz, 2H, ArH), 7.26 (td, 1H, ArH), 7.10 (dd, 1H, ArH), 6.74 (dd, 1H, ArH), 6.60 (td, 1H, ArH), 6.59 (d, J = 8.7 Hz, 2H, ArH), 6.50 (s, 2H, ArH), 5.03 (m, 1H, CH-4), 1.19 (m, 1H, CH-3), 2.95-2.70 (m, 4H, CH_2N-2,7), 1.91-1.60 (m, 4H, CH_2-5,6); IR (KBr) cm^{-1} 3434, 1700, 1623, 1610, 1542; low resolution FAB: (M + 1) 507.

Trans-3-[3,5-dihydroxy-4-(2-hydroxyphenylcarbonyl)]benzamido-4-(4-hydroxy)benzoyloxy-N-is propylperhydroazepine (COMPOUND 549)

To a solution of trans-N-benzyl-3-[3,5-dibenzyloxy-4-(2-benzyloxy)phenylcarbonyl]benzamido-4-(4-benzyloxy)-benzoyloxyperhydroazepine (190 mg, 0.199 mmol) in EtOAc-MeOH (1:1, 30 ml) was introduced Pearlman's catalyst 20% $Pd(OH)_2$ (70 mg). The mixture was subjected to hydrogenolysis at 50 psi for 17 hours. The catalyst was carefully filtered off through a pad of celite and washed with MeOH. The filtrate was concentrated and chromatographed on silica gel, eluting with 5% MeOH in CH_2Cl_2. The title compound was obtained (500 mg, 50%); the Parr bottle was contaminated with acetone and acid. All spectra (^1H, ^{13}C, APT, DEPT, MS) and CHN analysis fully support the structure. ^1H NMR (DMSO-d_6) δ 11.95 (s, brs, 1H, OH), 10.25 (s, 1H, OH), 10.00 (s, 2H, 2OH), 8.20 (d, 1H, NH), 7.78 (d, J = 8.67 Hz, 2H, ArH), 753 (td, 1H, ArH), 7.26 (dd, 1H, ArH), 6.99 (d, 1H, ArH), 6.87 (t, 1H, ArH), 6.82 (d, J = 8.73 Hz, ArH), 6.74 (s, 2H, ArH), 5.01 (s, br, 1H, CH-4), 4.18 (s, br, 1H, CH-3), 2.90 (s, br, 1H, $CH(CH_3)_3$), 2.68 (s, br, 4H, CH_2N-2,7), 1.90 (s, br, 3H, CH_2-6, CH-5), 1.63 (s, br, 1H, CH-5), 1.00 (dd, 6H, $2CH_3$); ^{13}C NMR (DMSO-d_6 + D_2O) δ 55.02 ($CH-(CH_3)_3$), 18.66 and 18.40 ($(CH_3)_2CH$); high resolution FAB M + 1: 549.2224; calculated for $C_{30}H_{32}N_2O_8$: 549.2228. Anal. calcd. for $C_{30}H_{32}N_2O_8 \cdot 1.25\ H_2O$: C, 63.09; H, 6.09; N, 4.90. Found: C, 63.06; H, 5.95; N, 4.66.

anti-4-(3,5-Dihydroxy-4-(2-hydroxybenzoyl)-benzoylamino)hexahydro-3-(4-hydroxybenzoylamino)azepine, complex with water:acetonitrile (1:1.7:0.3) (COMPOUND 550)

(SYNTHESIS OF COMPOUND 550)

Syn-3-Aminohexahydro-4-hydroxy-1-phenylmethylazepin-2-one

A solution of 3-acetylaminohexahydro-1-phenylmethyl-azepin-2,4-dione (0.82 g, 3.0 mmol) in absolute ethanol (15 ml) was treated with sodium borohydride (0.23 g, 6 mmol) and stirred for 30 min, then treated with water (5 ml) and concentrated in vacuo. The aqueous residue was extracted with methylene chloride (3 x 25 ml) and the combined organic extracts were dried (Na_2SO_4), concentrated in vacuo, and taken up in 2:1 ethanol/water (7.5 ml). Concentrated hydrochloric acid (2.5 ml) was added. The mixture was refluxed for 2 h and partially concentrated, then diluted with water (25 ml). The aqueous acidic mixture was extracted with ether (25 ml). The aqueous solution was basified with 30% sodium hydroxide and extracted with methylene chloride (3 x 40 ml). The combined methylene chloride extracts were washed with water (25 ml), dried (Na_2SO_4), and concentrated in vacuo to a yellow solid, which was recrystallized from ethyl acetate to afford syn-3-aminohexahydro-4-hydroxy-1-phenylmethylazepin-2-one (0.42 g, 60%) as a white solid.

Syn-3-Aminohexahydro-4-hydroxy-1-phenylmethylazepine

A cooled (5°C) solution of lithium aluminum hydride/tetrahydrofuran (Aldrich, 1.0 N, 5.1 ml) under nitrogen was treated with syn-3-aminohexahydro-4-hydroxy-1-phenylmethylazepin-2-one (0.40 g, 1.7 mmol) in portions so that the pot temperature did not exceed 15°C. The mixture was refluxed for 6.5 h, cooled on an ice bath, and carefully treated with water (0.21 ml), 15% sodium hydroxide (0.21 ml), and water (0.63 ml). The suspension was allowed to stir for 5 days (optimal time is 2-5 hours). The suspension was filtered, and the filtrate was concentrated in vacuo and chromatographed

on silica gel (eluted with 90:8:2 methylene chloride/methanol/triethylamine). The appropriate fractions were concentrated in vacuo to afford syn-3-aminohexahydro-4-hydroxy-1-phenylmethylazepine (0.22 g, 58%) as a colorless oil.

Syn-Hexahydro-4-hydroxy-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine

A solution of 4-benzyloxybenzoic acid (0.183 g, 0.8 mmol) in anhydrous tetrahydrofuran (2 ml) and N,N-dimethylformamide (0.5 ml) was treated with N,N'-carbonyldiimidazole (0.15 g, 0.9 mmol) and stirred at room temperature for 1.5h. The solution was treated with syn-3-aminohexahydro-4-hydroxy-1-phenylmethylazepine (0.20 g, 0.9 mmol) in anhydrous tetrahydrofuran (1 ml). The mixture was stirred for 18 h, then concentrated in vacuo. The residue was taken up in 1N sodium carbonate (20 ml), and the aqueous mixture was extracted with toluene (2x25 ml) containing a little 2-propanol. The combined organic extracts were dried (Na_2SO_4) and the concentrated residue was flash chromatographed on silica gel (eluted with 3:1 ethyl acetate/hexane) to afford syn-hexahydro-4-hydroxy-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.17 g, 50%) as a viscous oil.

syn-4-Aminohexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine

A solution of syn-hexahydro-4-hydroxy-3-(4-phenylmethoxy)-benzoylamino-1-phenylmethylazepine (0.645 g, 1.5 mmol) in anhydrous tetrahydrofuran (3 ml) under nitrogen was cooled (ice bath, 5°C) and treated with triphenylphosphine (0.495 g, 1.8 mmol) and diethylazodicarboxylate (0.313 g, 1.8 mmol). The mixture was then treated dropwise over 15 min with a solution of diphenylphosphoryl azide (0.495 g, 1.8 mmol) in anhydrous tetrahydrofuran (3 ml). The reaction was stirred at room temperature for 18 h, then concentrated in vacuo, dissolved in a little methylene chloride, and passed through a short column of silica gel (eluted with 10% acetone/methylene chloride). The early fractions containing chromophoric

material were concentrated in vacuo and dissolved in ethanol/acetic acid/water (6:1:1, 12 ml), then treated with zinc powder (0.50 g, 7.5 mmol). After 30 min, the mixture was filtered and the filtrate was concentrated in vacuo. The residue was taken up in 1.0 N sodium hydroxide (40 ml), and the aqueous mixture was extracted with methylene chloride (3 x 35 ml). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to afford crude syn-4-aminohexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.76 g).

syn-4-(3,5-Bis(phenylmethoxy)-4-(2-phenylmethoxybenzoyl))-benzoylaminohexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (COMPOUND 628)

A solution of 2,2',6-tribenzyloxybenzophenone-4-carboxylic acid (0.545 g, 1.0 mmol) in anhydrous methylene chloride (3 ml) and N,N-dimethylformamide (0.1 ml) under nitrogen was treated with 2.0 N oxalyl chloride/methylene chloride (0.7 ml, 1.4 mmol) and stirred for one hour. The solution was concentrated in vacuo to a yellow solid, which was kept under high vaccuum for one hour. A solution of crude syn-4-aminohexahydro-3-(4-phenylmethoxy)-benzoylamino-1-phenylmethylazepine (0.76 g, from above) in methylene chloride (5 ml) was added to the acid chloride above, followed by 1.0 N sodium hydroxide (4 ml). The mixture was stirred for 1.5 h, diluted with methylene chloride (15 ml) and separated. The aqueous layer was extracted with methylene chloride (15 ml) and the combined organic solution was washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel (eluted initially with 2.5% acetone/methylene chloride, then with 7.5% acetone/methylene chloride) to afford syn-4-(3,5-bis(phenylmethoxy)-4-(2-phenylmethoxy-benzoyl))-benzoylaminohexahydro-3-(4-phenylmethoxy)-benzoylamino-1-phenylmethylazepine (0.52 g, 54%) as an opaque gum.

syn-4-(3,5-Dihydr xy-4-(2-hydr xybenzoyl)-b nz ylamino)hexahydr -3-(4-hydroxybenzoylamin)azepine, complex with water:acetonitrile (1:1.7:0.3) (COMPOUND 550)

A solution of syn-4-(3,5-bis(phenylmethoxy)-4-(2-phenylmethoxybenzoyl))benzoylaminohexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.39 g, 0.41 mmol) in ethanol/ethyl acetate (1:1, 30 ml) was placed in a Parr bottle and treated (under nitrogen) with Pearlman's catalyst (Aldrich, 150 mg), then subjected to hydrogenation in a Parr apparatus for 18 h at 48-50 psi. The reaction mixture was carefully purged of hydrogen and the solution was filtered through celite (care taken not to let filter cake dry). The filtrate was concentrated in vacuo to afford crude material, which was chromatographed on silica gel (eluted with 2:1 methylene chloride/isopropanol) to give syn-4-(3,5-dihydroxy-4-(2-hydroxybenzoyl)benzoylamino)hexahydro-3-(4-hydroxybenzoylamino)azepine, complex with water:acetonitrile (1:1.7:0.3) (0.055 g, 27%) as a yellow solid, which was triturated with acetonitrile to afford a yellow powder: mp 210 - 215°C; Rf (2:1 methylene chloride/isopropanol on silica) 0.50; IR (KBr) 1624 cm^{-1}; ^1H NMR (d_6-DMSO) δ 8.33 (d, 1H, J = 7 Hz), 7.97 (d, 1H, J = 7 Hz), 7.73 (d, 2H, J = 9 Hz), 7.55 (m, 1H), 7.30 (m, 1H), 7.00 (m, 1H), 6.89 (m, 1H), 6.84 (s, 2H), 6.82 (d, 2H, J = 9 Hz), 4.25 - 4.40 (m, 2H), 3.00 - 3.10 (m, 2H), 2.80 - 3.00 (m, 2H), 1.85 - 1.95 (m, 1H), 1.65 - 1.80 (m, 3H). Anal. calcd. for $C_{27}H_{27}N_3O_7 \cdot 1.7H_2O \cdot 0.3(CH_3CN)$: C, 60.44; H, 5.75; N, 8.43. Found: C, 60.34; H, 5.56; N, 8.42.

Hexahydro-3-(4-phenylm thoxy)benzoylamino-1-phenylmethyl-azepin-4-one (COMPOUND 551)

A 25 ml 3-neck round bottom flask under nitrogen was charged with 2.0 N oxalyl chloride/methylene chloride (Aldrich, 1.125 ml, 2.25 mmol), diluted with anhydrous methylene chloride (2 ml), cooled (-65°C), and treated dropwise with anhydrous dimethylsulfoxide (0.35 g, 4.5 mmol) in anhydrous methylene chloride (1.2 ml) at a rate to keep the pot temperature below -60°C. The mixture was stirred at -65 ± 5°C for 30 min, then treated dropwise with a solution of syn-hexahydro-4-hydroxy-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.645 g, 1.5 mmol) in anhydrous methylene chloride (1.5 ml) at a rate to keep the pot temperature below -55°C. The mixture was stirred at 55 ± 5°C for 2 h, then treated dropwise with triethylamine (1.5 ml), warmed to room temperature over 1 h, and diluted with methylene chloride (10 ml). The organic solution was washed with water (10 ml), saturated aqueous sodium bicarbonate (10 ml), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel (eluted with 5% acetone/methylene chloride) to afford hexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepin-4-one (0.53 g, 82%) as a viscous colorless oil.

4-Aminohexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine, 1:1 mixture of syn and anti isomers

A solution of hexahydro-3-(4-phenylmethoxy)-benzoylamino-1-phenylmethylazepin-4-one (0.37 g, 0.86 mmol) in ethanol (5 ml) was treated with hydroxylamine hydrochloride (80 mg, 1.15 mmol) and 25% methanolic sodium methoxide (Aldrich, 70 mg, 0.32 mmol) and heated to 50°C for 1 h. The mixture was cooled to room temperature, treated with additional 25% sodium methoxide (0.18 g, 0.83 mmol), then stirred for 10 min and partially concentrated in vacuo. The residue was taken up in 0.5 N sodium hydroxide (5 ml) and extracted with methylene chloride (3 x 15 ml). The combined organic extracts were washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and concentrated in vacuo. This residue was dissolved in 95%

ethanol (20 ml), treated with Raney Nickel (Aldrich, 1/4 teaspoon) in a Parr bottle, and subjected to hydrogenation at 30 psi for 2.25 h (more time needed). The solution was carefully evacuated of hydrogen, filtered through celite (do not allow to dry), and the filtrate was concentrated in vacuo and chromatographed on silica gel (eluted first with 15% methanol/methylene chloride, then with 25%, and finally with 33%) to afford 4-aminohexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine, 1:1 mixture of syn and anti isomers (0.15 g, 40%) as a viscous colorless oil which was stored under nitrogen.

anti-4-(3,5-Bis(phenylmethoxy)-4-(2-phenylmethoxybenzoyl))-benzoylaminohexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (COMPOUND 629)

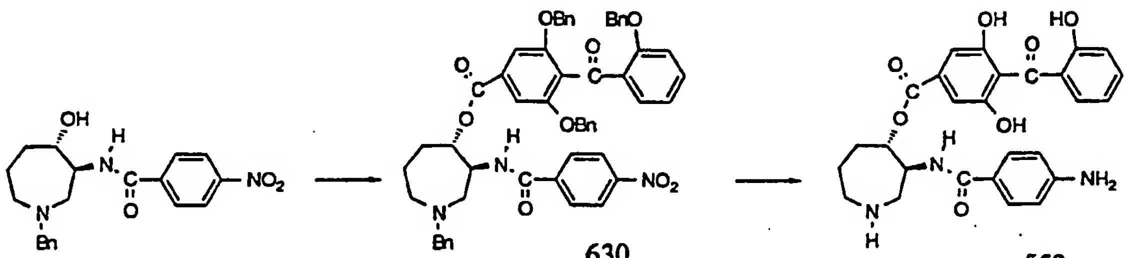
A solution of 2,6,2'-tribenzyloxybenzophenone-4-carboxylic acid (0.245 g, 0.45 mmol) in anhydrous methylene chloride (1.5 ml) under nitrogen was treated with N,N-dimethylformamide (3 drops), then with 2.0 N oxalyl chloride/methylene chloride (0.30 ml, 0.60 mmol). The vigorous bubbling soon subsided and the mixture was stirred for 1 h, concentrated in vacuo, and kept under high vacuum for 1 h to ensure removal of excess oxalyl chloride. The acid chloride was dissolved in methylene chloride (2.5 ml) and treated with 4-aminohexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine, 1:1 mixture of syn and anti isomers (0.14 g, 0.325 mmol) followed by 1.0 N sodium hydroxide (1.5 ml). The biphasic mixture was rapidly stirred for 2 h and separated. The aqueous layer was extracted with methylene chloride (2 x 7 ml), and the combined organic extracts and organic layer were washed with saturated aqueous sodium chloride (10 ml), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography on silica gel (eluted first with 3% acetone/methylene chloride, then with 7%, and finally with 10%) afforded anti-4-(3,5-bis(phenylmethoxy)-4-(2-phenylmethoxy-benzoyl))-benzoylaminohexahydro-3-(4-phenylmethoxy)benzoylamino-1-

phenylmethylazepine (0.13 g, 42%) as a colorless foam, followed by the syn isomer (0.13 g, 42%).

anti-4-(3,5-Dihydroxy-4-(2-hydroxybenzoyl)benzoylamino)hexahydro-3-(4-hydroxybenzoylamino)azepine, complex with water:2-propanol (1:1.5:0.4) (COMPOUND 551)

A solution of syn-4-(3,5-bis(phenylmethoxy)-4-(2-phenylmethoxybenzoyl))benzoylaminohexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.13 g, 0.136 mmol) in ethanol/ethyl acetate (1:1, 25 ml) was placed in a Parr bottle and treated (under nitrogen) with Pearlman's catalyst (Aldrich, 120 mg), then subjected to hydrogenation in a Parr apparatus for 18 h at 50 psi. The reaction mixture was carefully purged of hydrogen and the solution was filtered through celite (care taken not to let filter cake dry). The filtrate was concentrated in vacuo to afford crude material, which was chromatographed on silica gel (eluted with 1:1 methanol/methylene chloride). This concentrated product was dissolved in 2-propanol, filtered to remove inorganic material, re-concentrated in vacuo, and triturated from ether to afford anti-4-(3,5-dihydroxy-4-(2-hydroxybenzoyl)-benzoylamino)hexahydro-3-(4-hydroxybenzoylamino)azepine complex with water:2-propanol (1:1.5:0.4) (56 mg, 75%) as a yellow powder: mp 207 - 210°C; Rf (2:1 methylene chloride/2-propanol on silica) 0.20; IR (KBr) cm^{-1} 1639, 1607; ^1H NMR (d_6-DMSO) δ 8.32 (d, 1H, J = 7 Hz), 7.96 (d, 1H, J = 7 Hz), 7.66 (d, 2H, J = 9 Hz), 7.52 (m, 1H), 7.27 (m, 1H), 6.97 (m, 1H), 6.86 (m, 1H), 6.77 (d, 2H, J = 9 Hz), 6.72 (s, 2H), 4.00 - 4.15 (m, 2H), 2.60 - 3.00 (m, 4H), 1.50 - 1.90 (m, 4H). Anal. calcd. for $C_{27}H_{27}N_3O_7 \circ 1.5\ H_2O \circ 0.4\ (C_3H_8O)$: C, 60.85; H, 6.01; N, 7.55. Found: C, 60.68; H, 5.68; N, 7.22.

(±)-Anti-3-(4-aminobenzamido)-4-[3,5-dihydroxy-4-(2-hydroxyphenylcarbonyl)]benzyl xyperhydroazepine (COMPOUND 552)



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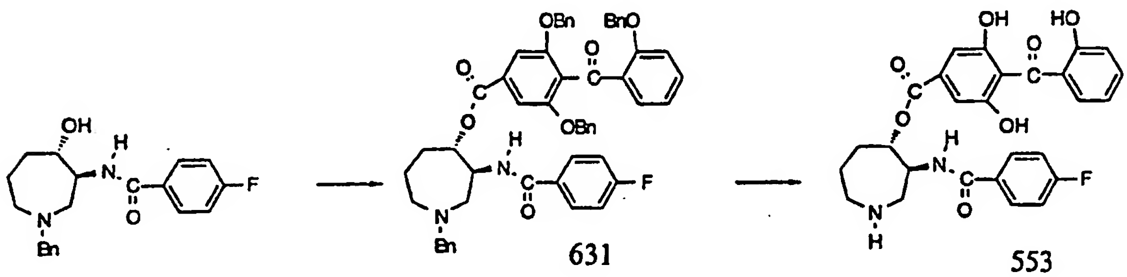
552

3,5-dibenzyloxy-4-[(2-benzyloxybenzoyl]benzoic acid (218 mg, 0.40 mmol) was dissolved in anhydrous dichloromethane (2.0 ml), and dimethylformamide (0.05 ml). The reaction was placed under nitrogen, and oxalyl chloride (0.3 ml, 2M in dichloromethane) was slowly added via a syringe. The reaction was stirred at room temperature for 1 h and then concentrated in vacuo and placed under high vacuum for 1 h. The residue was redissolved in anhydrous dichloromethane (2 ml) and stirred under nitrogen. Next, a solution of (±)-anti-3-(4-nitrobenzamido)-4-hydroxybenzylperhydroazepine (120 mg, 0.32 mmol) and dimethylaminopyridine (44 mg,0.36 mmol) in triethylamine (0.9 ml) and anhydrous dichloromethane (3 ml) were added. The reaction was then stirred for 1 h at room temperature. At this point, dichloromethane (50 ml) and 0.5 N sodium hydroxide (20 ml) were added, and the reaction was transferred to a separatory funnel. The aqueous layer was removed, and brine was added. The organic layer was then isolated, dried over sodium sulfate, filtered, and concentrated in vacuo to yield a yellow oil. The oil was flash chromatographed eluting with hexane:ethyl acetate/4:1. Pure fractions of the major product were concentrated in vacuo to yield 180 mg of white solid (COMPOUND 636). The solid was then dissolved in methanol:ethyl acetate/2:1 (30 ml) and acetic acid

(0.2 ml) in a 500 ml Parr bottle along with 5% palladium on activated carbon (70 mg). The Parr bottle was then placed on the Parr hydrogenator for 24 h. The reaction mixture was filtered to remove the catalyst, and then concentrated in vacuo to yield a yellow solid. The solid was flash chromatographed eluting with dichoromethane:methanol/9:1 to yield a yellow solid of the title compound (60 mg, 61%): mp 175 - 185°C; NMR (CD_3OD) consistant with structure; IR (KBr) cm^{-1} 3389 (OH); 2361 (alkyl); 1704 (ester); 1625 (ketone). Anal. calcd. for $C_{27}H_{27}N_3O_7 \circ 1.0\ H_2O \circ 1.0$ acetic acid: C, 59.69; H, 5.70; N, 7.20. Found: C, 59.94; H, 5.70; N, 7.31.

(±)-Anti-3-(4-fluorobenzamido)-4-[3,5-dihydr xy-4-(2-hydroxyphenylcarbonyl)]benzyloxyperhydr azepine (COMPOUND 53)

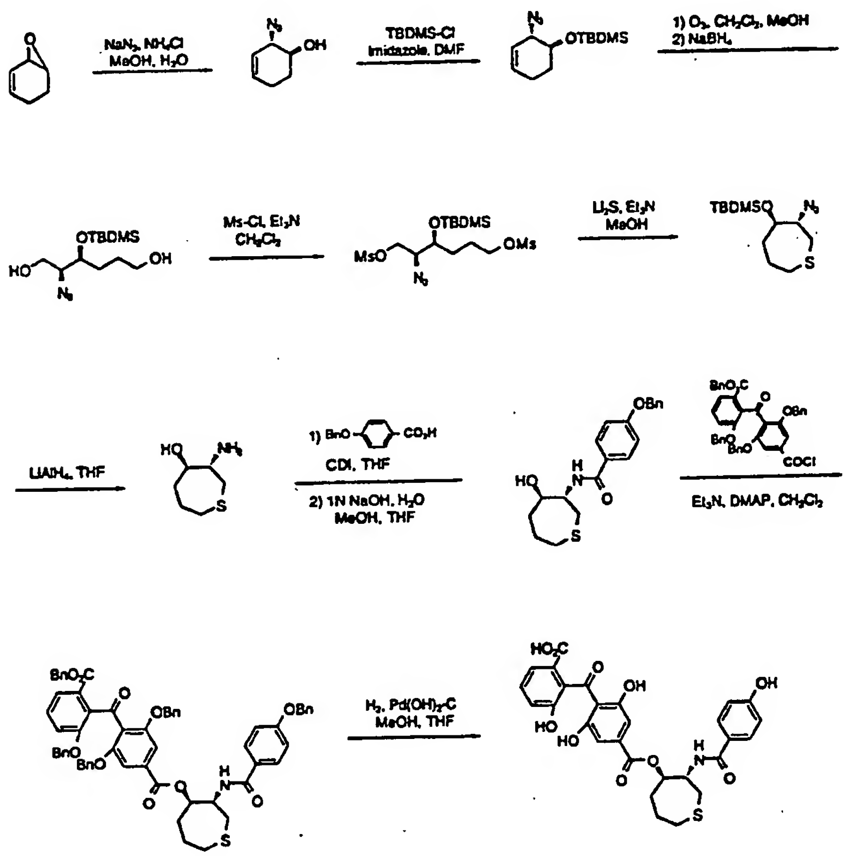


631 553

3,5-Dibenzyloxy-4-[(2-benzyloxybenzoyl]benzoic acid (545 mg, 1.0 mmol) was dissolved in anhydrous dichloromethane (5.0 ml), and dimethylformamide (0.05 ml). The reaction was placed under nitrogen, and oxalyl chloride (1.0 ml, 2 M in dichloromethane) was slowly added via a syringe. The reaction was stirred at room temperature for 2 h and then concentrated in vacuo and placed under high vacuum for 1.5 h. The residue was redissolved in anhydrous dichloromethane (3 ml) and stirred under nitrogen. Next, a solution of (±)-anti-3-(4-fluorobenzamido)-4-hydroxy-N-benzylperhydroazepine (300 mg, 0.93 mmol) and dimethylaminopyridine (125 mg, 1.02 mmol) in triethylamine (0.9 ml) and anhydrous dichloromethane (2 ml) were added. The reaction was then stirred for 20 min at room temperature. At this point, dichloromethane (50 ml) and 0.5 N sodium hydroxide (30 ml) were added, and the reaction was transfered to a separatory funnel. The aqueous layer was removed, and brine was added. The organic layer was then isolated, dried over sodium sulfate, filtered, and concentrated in vacuo to yield a light brown foam. The foam was flash chromatographed eluting with hexane:ethyl acetate/2:1. Pure fractions of the major product were concentrated in vacuo to yield 440 mg of white solid (COMPOUND 631). 260 mg of the

solid was dissolved in methanol:ethyl acetate/5:1 (30 ml) and acetic acid (0.2 ml) in a 500 ml Parr bottle along with 5% palladium on activated carbon (100 mg). The Parr bottle was then placed on the Parr hydrogenator for 4.5 h. The reaction mixture was filtered to remove the catalyst, and then concentrated in vacuo to yield a yellow solid. The solid was flash chromatographed eluting with dichoromethane:methanol/8:2 to yield a yellow solid of the title compound (110 mg, 72%): mp 189°C; IR (KBr) cm^{-1} 3349 (OH); 2362 (alkyl); 1704 (ester); 1626 (ketone). Anal. calcd. for $C_{27}H_{25}N_2O_7F \circ 1.0\ H_2O \circ 1.0$ acetic acid: C, 59.38; H, 5.33; N, 4.78. Found: C, 59.09; H, 5.00; N, 4.71.

Trans-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-hydroxycarbonyl-benzoyl)-3,5-dihydr xybenzoyloxyl]perhydr thi pine (COMPOUND 554)



632

554

A mixture of 1,3-cyclohexadienemonoepoxide (9.61 g, 100 mmol, for preparation see: J. K. Crandall *et al.*, *J. Org. Chem.*, **1968**, *33*, 423), NaN_3 (26 g, 400 mmol), NH_4Cl (10.7 g, 200

mmol), MeOH (300 ml), and H_2O (50 ml) was stirred at 65°C for 16h. The resultant slurry was evaporated to remove all the volatile materials and the residue was treated with 1 N NaOH (100 ml), and extracted with CH_2Cl_2 (3 x 60 ml). The combined CH_2Cl_2 extracts were washed with H_2O (2 x 100 ml), dried ($MgSO_4$), evaporated, and chromatographed on a SiO_2 column (Et_2O:hexane = 1:4) to give a colorless oil (7.308 g, 53%).

A mixture of the product of the previous reaction (7.23 g, 52 mmol), TBDMS-Cl (8.227 g, 55 mmol), and imidazole (5.308 g, 78 mmol) in N,N-dimethylformamide (50 ml) was stirred at room temperature for 16h. Et_2O (250 ml) was added and the resultant mixture was washed with H_2O (5 x 100 ml), dried ($MgSO_4$), and evaporated to give a colorless oil (12.76 g, 97%) which was used in the next step without further purification.

A solution of oil (7.63 g, 30 mmol) in MeOH (150 ml) and CH_2Cl_2 (30 ml) was cooled to -78°C, stirred, and treated with a mixture of air and O_3 until a blue color persisted (ca. 1.5h). Excess O_3 was removed by bubbling N_2 through the solution, and then $NaBH_4$ (4.54 g, 120 mmol) was added. After being stirred at -78°C for 30 min. followed by 30 min. at room temperature the resultant mixture was poured into 1 N HCl (100 ml) and then evaporated to remove the volatile components. The aqueous residue was extracted with Et_2O (4 x 50 ml), and the combined ether extracts were washed with H_2O (100 ml), brine (100 ml), dried ($MgSO_4$), evaporated, and crystallized from Et_2O:hexane to give a white solid (6.772 g, 78%).

Methanesulfonyl chloride (2.67 ml, 34 mmol) was added dropwise to a stirred solution of the borohydride reduction product (4.01 g, 14 mmol) and Et_3N (5.76 ml, 41 mmol) in CH_2Cl_2 (40 ml) at 5°C. After 30 min. the cooling bath was removed and stirring was continued for 16h. The resultant mixture was diluted with CH_2Cl_2 (20 ml), washed with 1 N HCl (3 x 30 ml), H_2O (2 x 30 ml), brine (2 x 30 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2, Et_2O:hexane = 1:1 followed by Et_2O:hexane:CH_2Cl_2 = 1:1:0.25) to give a pale yellow oil (5.885 g, 96%).

A mixture of the product of the previous reaction (2.24 g, 5 mmol), lithium sulfide (253 mg, 5.5 mmol), and Et_3N (2.09 ml, 15 mmol) in EtOH (100 ml) was stirred under reflux for 16h. The resultant mixture was evaporated and the residue was chromatographed (SiO_2, Et_2O:hexane = 1:30) to give a colorless oil (515 mg, 36%).

A solution of $LiAlH_4$ in Et_2O (1 M, 3.58 ml) was added to the colorless oil from the reaction above (515 mg, 1.79 mmol) in Et_2O (9 ml) and the mixture was stirred at room temperature for 2h. 5N aq NaOH (5 ml) was added cautiously and stirring was continued at room temperature for 16h. The phases were separated and the aqueous phase was saturated with NaCl and extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layers were dried ($MgSO_4$), and evaporated to give a colorless oil which solidified on standing (250 mg, 95%). This material was used in the next step without further purification.

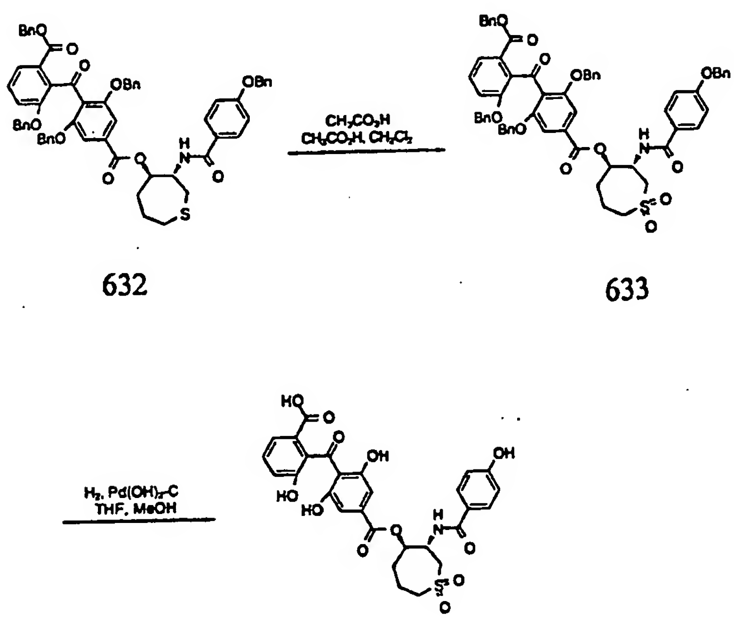
A mixture of 4-benzyloxybenzoic acid (427 mg, 1.87 mmol) and 1,1'-carbonyldiimidazole (302 mg, 1.87 mmol) in THF (5 ml) was stirred at room temperature for 2h and then the product of the previous reaction (250 mg, 1.70 mmol) in THF (5 ml) was added. The mixture was stirred at room temperature for 36h, evaporated, dissolved in CH_2Cl_2 (30 ml), washed with H_2O, and dried ($MgSO_4$). The resultant solution was diluted with hexane (10 ml) and rotaevaporated at 0°C to ca. 10 ml. The white precipitate was collected, dried under vacuum, and dissolved in a mixture of MeOH (10 ml) and THF (8 ml). 1 N aq. NaOH (1 ml) was added and the mixture was stirred at room temperature for 4h. The volatile components were evaporated and the residue was dissolved in CH_2Cl_2 (25 ml), washed with H_2O (3 x 5 ml), dried ($MgSO_4$), and filtered. The filtrate was diluted with hexane (10 ml) and rotaevaporated at 0°C to ca. 5 ml. The precipitate was collected, washed with hexane, and dried under vacuum to give a white powder (382 mg, 67%).

To a solution of 4-(2-benzyloxy-6-benzyloxycarbonyl-benzoyl)-3,5-dibenzyloxybenzoic acid (305 mg, 0.45 mmol) and a drop of N,N-dimethylformamide in CH_2Cl_2 (1.3 ml) at 5°C was

added a solution of oxalyl chloride in CH_2Cl_2 (2 M, 0.25 ml). The resultant mixture was stirred at room temperature for 2h and then evaporated. The residue was dried under vacuum for 2h, dissolved in CH_2Cl_2 (0.8 ml), and added to a mixture of the above intermediate (143 mg, 0.4 mmol), Et_3N (61 mg, 0.6 mmol), and 4-N,N- dimethylaminopyridine (5 mg, 0.04 mmol) in CH_2Cl_2 (1.2 ml). The resultant solution was stirred at room temperature for 17h, diluted with CH_2Cl_2 (10 ml), washed with H_2O (3 x 5 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2, Et_2O:hexane:CH_2Cl_2 = 1:1:0.5) to give a colorless oil (347 mg, 76%).

This intermediate (105 mg, 0.1 mmol), $Pd(OH)_2$ on carbon (20 wt%, contains $\geq$ 50% moist, 281 mg, 0.2 mmol), THF (1 ml), and MeOH (1 ml) was stirred and treated with 1 atm H_2 at room temperature for 40h. The resultant mixture was filtered through a Florisil pad and the Florisil pad was washed with MeOH (15 ml). The combined filtrate and wash were evaporated to give a yellow solid (25 mg, 35%) (COMPOUND 554). IR (KBr, cm^{-1}): 1706, 1689, 1633.

1,1-Dioxo-trans-3-(4-hydr xybenzamido)-4-[4-(2-hydroxy-6-hydroxycarb nylb nzoyl)-3,5-dihydr xybenzoyl xyl]-perhydrothiepine (COMPOUND 555)



632

633

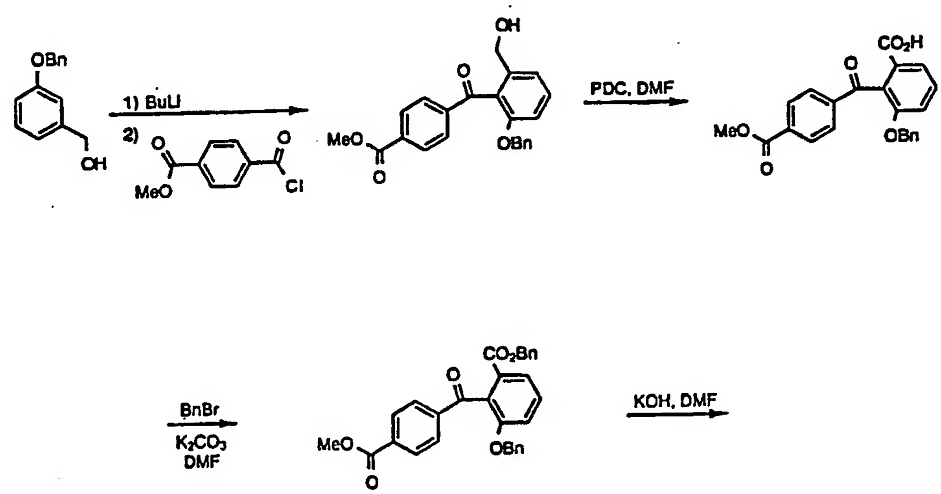
555

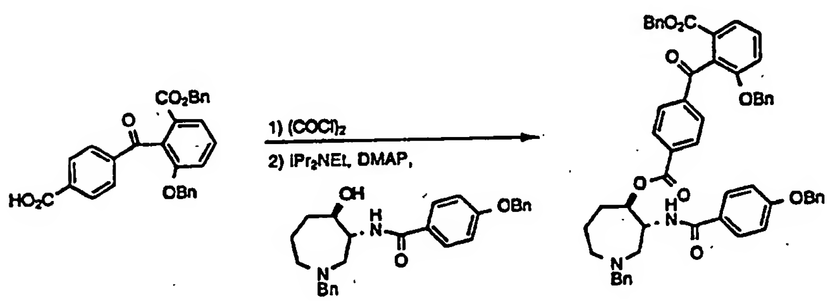
Figure AA

Peroxyacetic acid (32 wt% in acetic acid, 37 mg, 0.155 mmol) was added to a solution of Compound 632 (75 mg, 0.074 mmol, see Compound 554 for preparation) in CH_2Cl_2 (0.7 ml). The resultant mixture was stirred at room temperature for 1h, diluted with CH_2Cl_2 (10 ml), and washed with sat. aq. K_2CO_3 (3 x 5 ml). The organic layer was dried ($MgSO_4$) and evaporated to give a white solid which was recrystallized from hot EtOAc (10 ml, contains ca. 2 ml of THF and 3 ml of hexane) to give a white powder (61 mg, 79%) (COMPOUND 633).

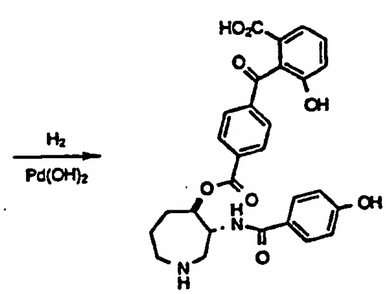
A mixture of Compound 633 (61 mg, 0.058 mmol), $Pd(OH)_2$ on carbon (20 wt%, contains $\geq$ 50% moist, 8 mg, 0.0058 mmol), THF (1 ml), and MeOH (1 ml) was stirred and treated with 1 atm H_2 at room temperature for 3 hr. The resultant mixture was filtered through Florisil and the filtrate was evaporated to give the title compound as a yellow solid (33 mg, 95%). IR (KBr, cm^{-1}): 1718, 1686, 1635.

Trans-4-(4-(2-Carboxy-6-hydroxybenzoyl)benzoyloxy)-3-(4-hydroxybenzamido)perhydroazepine Trifluoroacetic Acid Salt Hydrate (COMPOUND 556)





634



556

Methyl-4-(6-Benzyloxy-2-hydroxym thylbenzoyl)benzoate

To a solution of 1.07 g (5.00 mmol) of 3-benzyloxybenzyl alcohol in 15 ml of toluene at -5°C under an atmosphere of nitrogen was added 5.8 ml (12.2 mmol) of a 2.1 M solution of butyllithium in hexanes over 15 min. The solution was stirred at -5°C for 6 h, after which it was cooled to -78°C, and a solution of 1.00 g (5.03 mmol) of 4-(methoxycarbonyl)benzoyl chloride in 5 ml of tetrahydrofuran was added. The mixture was stirred for 1 h, after which it was poured onto 200 ml of ether and 100 ml of saturated aqueous ammonium chloride, and this mixture was stirred for 10 min. The layers were separated, and the organic phase was washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated to give the crude product. Flash chromatography on silica gel eluting with 3/1 ethyl acetate -hexane afforded 0.68 g (36%) of the title compound as a white solid, which was carried on to the next step.

Methyl-4-(6-Benzyloxy-2-carboxybenzoyl)benzoate

To a solution of 0.63 g (1.7 mmol) of methyl 4-(6-benzyloxy-2-hydroxymethylbenzoyl)benzoate in 20 ml of dimethylformamide was added 4.41 g (11.7 mmol) of pyridinium dichromate. The solution was stirred at room temperature under a nitrogen atmosphere for 4 days, after which it was poured onto 300 ml of ether and washed with 200 ml of water, 150 ml of 2 M HCl, and 150 ml of brine, and dried over magnesium sulfate. Evaporation of the solvent afforded 0.47 g (72%) of the crude product. This material was sufficiently pure for further use and was carried directly to the next step.

Methyl-4-(6-Benzyloxy-2-(benzyloxycarbonyl)benzoyl)benzoate

To a solution of 0.47 g (1.2 mmol) of methyl 4-(6-benzyloxy-2-carboxybenzoyl)benzoate in 20 ml of dry dimethylformamide was added 501 mg (3.62 mmol) of potassium carbonate and 0.158 ml (227 mg, 1.32 mmol) of benzyl bromide. The solution was stirred at room temperatur under a nitrogen atmosphere for 18 h. The mixture was then poured onto 300 ml

of ether and washed with two 200 ml portions of water and then with 150 ml of brine, and dried over magnesium sulfate. Evaporation of the solvent afforded 0.57 g of the crude product, which was chromatographed on silica gel, eluting with 3/1 hexane-ethyl acetate to give 0.32 g (54%) of the title compound as a colorless oil. This material was used directly in the next step.

4-(6-Benzyloxy-2-(benzyloxycarbonyl)benzoyl)benzoic Acid

A solution of 0.301 g (0.614 mmol) of methyl 4-(6-benzyloxy-2-(benzyloxycarbonyl)benzoyl)benzoate in 7 ml of DMF was treated with 0.337 ml of a 2 M aqueous solution of potassium hydroxide under an atmosphere of nitrogen for 20 h. The mixture was then poured onto 100 ml of ethyl acetate and washed with 60 ml each of 0.2N HCl, water, and brine. The organic extracts were dried over magnesium sulfate and evaporated to give 0.32 g of the crude product, which was chromatographed on a 41 x 250 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0-100% B over 60 min, flow: 25 ml/min). The pure fractions were pooled and evaporated and then lyophilized from water to give 70 mg of the title compound as a white solid, which was carried on as is to the next step.

Trans-N-Benzyl-4-(4-(6-benzyloxy-2-(benzyloxycarbonyl)benzoyl)benzoyloxy)-3-(4-benzyloxybenzamido)perhydroazepine

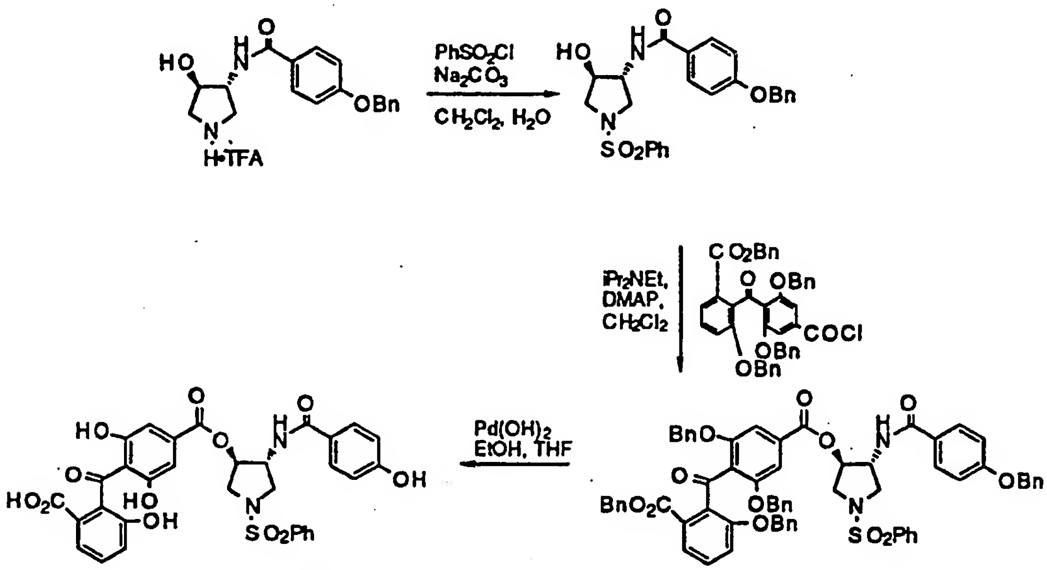
A solution of 68 mg (0.143 mmol) of 4-(6-benzyloxy-2-(benzyloxycarbonyl)benzoyl)benzoic acid in 5 ml of methylene chloride containing a trace (approximately 1 μL) of dimethylformamide was cooled to 0°C. A 2.0 M solution of oxalyl chloride (0.11 ml, 0.22 mmol) was added, and the mixture was stirred under a nitrogen atmosphere for 2 h. An additional 0.17 ml of oxalyl chloride was added, and the mixture was stirred for an additional 2 h. The reaction mixture was evaporated, and the residue was evaporated twice from 10 ml of methylene chloride. The residue was dissolved in 3 ml of methylene chloride, and was added to a solution of 69.6 mg

(0.162 mmol) of trans-N-benzyl-3-(4-benzyloxybenzamido)-4-hydroxyazepine, 29.8 µL (0.17 mmol) of diisopropylethylamine, and 5.4 mg of DMAP in 5 ml of methylene chloride at 0°C. The mixture was stirred at room temperature under a nitrogen atmosphere for 17 h, after which it was diluted with 30 ml of methylene chloride, washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated to give 146 mg of the crude product. Chromatography on silica gel eluting with 1/1 hexane-ethyl acetate gave 46 mg (37%) of the title compound as a yellow oil, which was taken directly to the next step.

Trans-4-(4-(2-Carboxy-6-hydroxybenzoyl)benzoyloxy)-3-(4-hydroxybenzamido)perhydroazepine Trifluoroacetic Acid Salt Hydrate

A solution of 46 mg (0.052 mmol) of trans-N-benzyl-4-(4-(6-benzyloxy-2-(benzyloxycarbonyl)benzoyl)benzoyloxy)-3-(4-benzyloxybenzamido)azepine in 10 ml of ethanol was treated with 8.1 µL of trifluoroacetic acid, cooled to 0°C, and 22 mg of moist 10% palladium hydroxide on carbon was added. The mixture was then stirred under an atmosphere of hydrogen for 19 h at room temperature. The mixture was filtered, evaporated, and the residue was chromatographed on a 21 x 250 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0-50% B over 60 min, flow: 15 ml/min). The pure fractions were pooled and evaporated and then lyophilized from water to give 9.8 mg (28%) of the title compound as a white fluffy solid. FABMS: m/z 519 (M + H). Anal. Calc. for $C_{28}H_{26}N_2O_8 \circ 2.5\ H_2O \circ$ TFA; C, 53.18 H, 4.76; N, 4.13. Found: C, 53.43; H, 4.64; N, 4.30

Trans 4-[4-(2-Hydroxycarbonyl-6-hydroxybenz yl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)-1-(phenylsulf nyl)-pyrrolidine (COMPOUND 562)



562

639

Figure AC

(±)-Trans-3-(4-benzyloxybenzamido)-4-hydroxy-1-(phenylsulfonyl)pyrrolidine

To a slurry of (±)-Trans-3-(4-benzyloxybenzamido)-4-hydroxypyrrolidine • TFA (150 mg, 0.352 mmol) in H_2O (8.8 ml) and CH_2Cl_2 (8.8 ml) were added anhydrous Na_2CO_3 (112 mg, 3.0 eq, 1.06 mmol) then benzene sulfonyl chloride (58 μl, 0.458 mmol, 1.3 eq), and the mixture stirred at room temperature 15 h. The solution was then diluted with CH_2Cl_2 (20 ml) and poured into H_2O (20 ml) and methanol (4 ml). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 30 ml). The organics were combined, dried ($MgSO_4$), filtered and evaporated to a white powder (159 mg, quant yield): ^{1}H NMR (CD_3OD) δ 7.62 (d, J = 7.7 Hz, 2H), 7.43 (d, J = 8.9 Hz, 2H), 7.35-7.30 (m,

3H), 7.25-7.10 (m, 5H), 6.80 (d, J = 8.8 Hz, 2H), 4.95 (s, 2H), 4.06-4.00 (m, 1H), 3.95-3.90 (m, 1H), 3.50-3.35 (m, 2H), 3.15 (dd, J = 10.6, 3.9 Hz, 1H), 2.99 (dd, J = 10.8, 3.2 Hz, 1H).

(±)-Trans-4-[4-(6-benzyloxy-2-(benzyloxycarbonyl)benzoyl]-3,5-dibenzyloxybenzoyloxy)-3-(4-benzyloxybenzamido)-1-(phenylsulfonyl)pyrrolidine (COMPOUND 639)

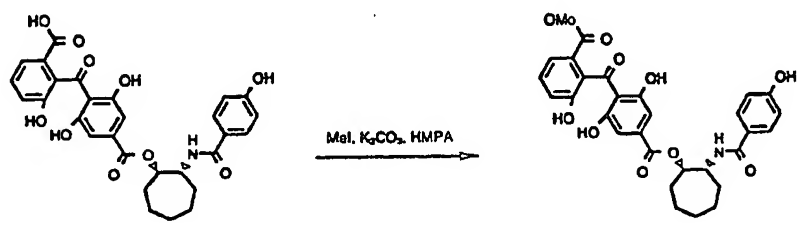
To a solution of the previous product (159 mg, 0.352 mmol) in CH_2Cl_2 (6.0 ml) were added 4-dimethylaminopyridine (43 mg, 0.352 mmol, 1.0 eq), diisopropylethylamine (74 μl, 0.42 mmol, 1.2 eq) then a solution of acid chloride (0.383 mmol, 1.1 eq) in CH_2Cl_2 (3.0 ml). The mixture was stirred at room temperature under N_2 14 h. The reaction mixture was then diluted with CH_2Cl_2 (30 ml), and washed with 10% $NaHCO_3$ (50 ml) then brine (50 ml). The aqueous layers were combined and extracted with CH_2Cl_2 (2 x 50 ml). The organics were combined, dried ($MgSO_4$), filtered and evaporated. Flash column chromatoghraphy of the residue (2:1 hexane:ethyl acetate) on silica gel provided the title compound (183 mg, 47%): ^{1}H NMR ($CDCl_3$) δ 7.77 (d, J = 6.7 Hz, 2H), 7.70 (d, J = 8.8 Hz, 2H), 7.47-7.16 (m, 14H), 7.15-7.05 (m, 6H), 7.04-6.94 (m, 3H), 6.90-6.83 (m, 3H), 6.42 (d, J = 6.7 Hz, 1H), 5.30 (dt, J = 5.1, 2.6 Hz, 1H), 5.18 (s, 2H), 5.13 (s, 2H), 4.78 (m, 2H), 4.76 (s, 2H), 4.72 (s, 2H), 4.64-4.60 (m, 1H), 3.88 (dd, J = 12.6, 5.4 Hz, 1H), 3.74-3.65 (m, 1H), 3.60-3.38 (m, 2H).

(±)-Trans 4-[4-(2-Hydroxycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)-1-(phenylsulfonyl)-pyrrolidine (COMPOUND 562)

To a solution of the previous product (183 mg, 0.164 mmol) in THF (7.4 ml) and ethanol (7.4 ml) was added $Pd(OH)_2$ (92 mg. of a 20% by weight powder). The flask was evacuated and filled with H_2 twice, then stirred under H_2 (1 atm) for 20 h. The suspension was filtered through Celite, washed through with methanol (50 ml), and evaporated to a yellow oil. Purification by HPLC (21 x 250 mm C_{18} column) provided the title compound (75 mg, 69%) as a fluffy yellow powder after

lyophilization: mp 185-208°C; IR (KBr) 3402, 1709, 1636, 1608, 1232 cm^{-1}; ^{1}H NMR (CD_3OD) δ 7.53 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 7.3 Hz, 1H), 7.22-7.11 (m, 3H), 7.09 (dd, J = 8.1, 7.9 Hz, 1H), 6.84 (d, J = 7.2 Hz, 1H), 6.61 (d, J = 8.7 Hz, 2H), 6.35 (s, 2H), 4.99 (app t, J = 2.2 Hz, 1H), 4.92 (dd, J = 5.6, 2.8 Hz, 1H), 3.62 (dd, J = 13.0, 4.3 Hz, 1H), 3.50 (dd, J = 10.8, 6.0 Hz, 1H), 3.39 (dd, J = 10.7, 2.4 Hz, 1H), 3.32 (bd, J = 13.1 Hz, 1H); HRMS (M + H) calcd 663.6315, found 663.1302; Anal. Calcd. for $C_{32}H_{26}N_2O_{12}S \cdot 1\ H_2O$: C, 56.47; H, 4.15; N, 4.12; S, 4.71; found: C, 56.56; H, 4.17; N, 4.09; S, 4.58.

Trans-1-(4-hydroxybenzamido)-2-[4-(2-hydroxy-6-methoxycarbonyl-benzoyl)-3,5-dihydroxybenzoyloxyl]cycloheptane (COMPOUND 566)

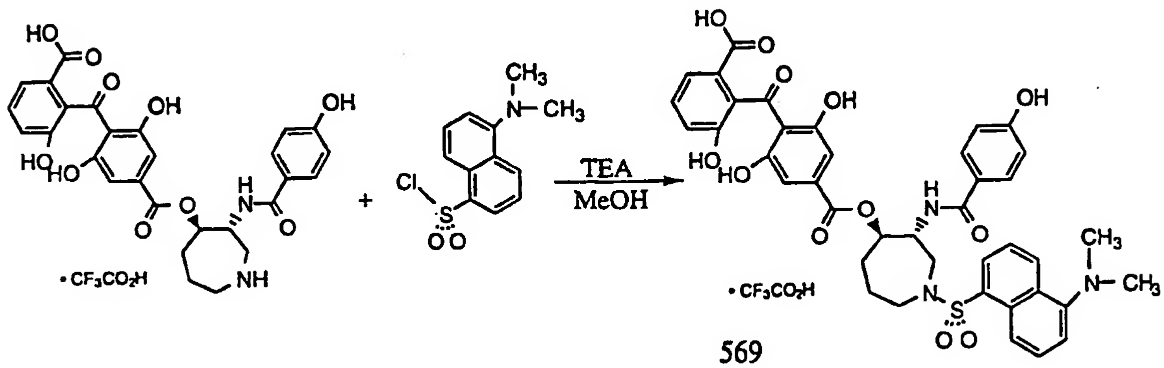


588 566

Figure AD

A mixture of Compound 588 (55 mg, 0.1 mmol), iodomethane (0.05 ml. 0.8 mmol), and K_2CO_3 (28 mg, 0.2 mmol) in HMPA (0.2 ml) was stirred at 40°C for 1.5h, and the reaction was judged incomplete by TLC. Additional iodomethane (0.025 ml, 0.4 mmol) was added and stirring was continued for 2h. at 40°C. EtOAc (15 ml) was added and the resultant mixture was washed with H_2O (3 x 10 ml) and brine (10 ml), dried ($MgSO_4$), and evaporated. The residue was purified by preparative TLC (SiO_2, multi-elution with CH_2Cl_2:5% MeOH in EtOAc = 4:1) to give a yellow solid (34 mg, 61%). IR (KBr, cm^{-1}): 1712, 1634, 1607. FBMS: M/Z = 564 (M + 1).

(±)-Trans-4-[4-(2-Hydroxycarbonyl-6-hydroxybenzoyl)-3,5-dihydr xybenzoyloxy]-3-(4-hydroxybenzamido)-1-(5-dim thylamino-1-naphthalen sulfonyl)perhydroazepine (COMPOUND 569)

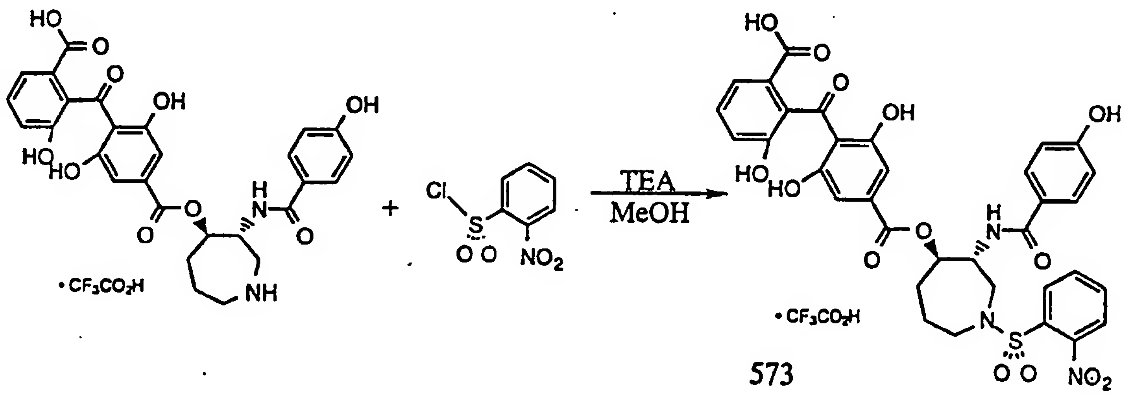


569

Racemic balanol (preparation described in Compound 508; 100 mg, 147 μmol) was dissolved in methanol (1 ml) and treated with triethylamine (204 μl, 1.47 μmol) and dansyl chloride (39.5 mg, 146.5 μmol) in methylene chloride (1 ml). After stirring at room temperature for 3 h, the mixture was concentrated under vacuum to a yellow film. The residue was dissolved in DMF (2 ml) and chromatographed on a Dynamax-60 C_{18} column (41 mm ID x 25 cm length) using a linear gradient from 100% A (0.1% TFA and 5% acetonitrile in water) to 100% B (pure acetonitrile) over 60 m at 25 ml/min. The clean product, which eluted in 40 m, was freeze-dried to give a yellow powder (33 mg, 29%): m.p. 185-187°C dec; ^{1}H-NMR (DMSO, 300 MHz) δ 1.73-2.12 (4H, m), 2.85 (6H, s), 4.30-4.41 (1H, m), 5.20 (1H, pseudo t), 6.75-6.87 (4H, m), 7.07 (1H, d, J = 8 Hz), 7.30 (2H, t), 7.39 (1H, d, J = 8 Hz), 7.62-7.70 (4H, m), 8.06 (1H, d, J = 8 Hz), 8.24 (1H, d, J = 9 Hz), 8.50 (1H, d, J = 9 Hz), 9.91 (1H, s), 11.68 (1H, s); IR (KBr): cm^{-1} 3399, 2361, 2340, 1702, 1677, 1635, 1607, 1542, 1507, 1462, 1425, 1371, 1319, 1283, 1237, 1200, 1139, 1103, 1064, 991, 920, 848, 793, 767, 723, 669, 581, 542, 532. Anal. Calcd. for $C_{40}H_{37}N_3O_{12}S \cdot 2H_2O \cdot .92TFA$

• .15CH_3CN: C, 54.37; H, 4.58; N, 4.73; S, 3.44. Found: C, 57.35; H, 4.51; N, 4.63; S, 3.17. LRMS (FAB) m/z 784.0 (783.2 calcd for $C_{40}H_{37}N_3O_{12}S$).

(±)-Trans-4-[4-(2-Carb xy-6-hydroxyb nzoyl)-3,5-dihydr xybenzoyloxy]-3-(4-hydroxybenzamido)-1-(2-nitrobenzenesulfonyl)perhydroazepin , trifluoracetic acid salt (COMPOUND 573)



Racemic balanol (preparation described in Compound 508; 100 mg, 147 μmol) was dissolved in methanol (1 ml) and treated with triethylamine (204 μl, 1.47 μmol) and 2-nitrobenzene sulfonyl chloride (48.7 mg, 219.7 μmol) in methylene chloride (1 ml). After stirring at room temperature for 3 h, the mixture was concentrated under vacuum to a yellow film. The residue was dissolved in DMF (2 ml) and chromatographed on a Dynamax-60 C_{18} column (41 mm ID x 25 cm length) using a linear gradient from 100% A (0.1% TFA and 5% acetonitrile in water) to 100% B (pure acetonitrile) over 60 m at 25 ml/min. The clean product, which eluted in 33 m, was freeze-dried to give a yellow powder (28 mg, 26%): m.p. 158-160°C dec; ^{1}H-NMR (DMSO, 300 MHz) δ 1.81-1.97 (3H, m), 2.06-2.17 (1H, m), 4.43-4.57 (1H, m), 5.18-5.28 (1H, m), 6.75 (2H, s), 7.04 (1H, d, J = 8 Hz), 7.22-7.31 (3H, m), 7.36 (1H, d, J = 8 Hz), 8.05 (1H, t), 8.20 (1H, d, J = 8 Hz), 8.20 (1H, d, J = 8 Hz), 8.85 (1H, d, J = 8 Hz), 9.87 (1H, s), 11.67 (1H, s); IR (KBr): cm^{-1} 3430, 3412, 1701, 1676, 1636, 1604, 1545,

1496, 1425, 1370, 1290, 1237, 1201, 1148, 1104, 1063, 1016, 993, 921, 874, 856, 799, 761, 738, 724, 586. Anal. Calcd. for $C_{34}H_{29}N_3O_{14}S \circ 1.2\ H_2O \circ 1.1$ TFA: C, 49.25; H, 3.71; N, 4.76; S, 3.63. Found: C, 49.22; H, 3.70; N, 4.72; S, 3.39. LRMS (FAB) m/z 735.9 (735.68 calcd for $C_{34}H_{29}N_3O_{14}S$).

(±)-Trans-4-[4-(2-Carboxy-6-hydroxybenz yl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)-1-(4-nitrobenz n sulfonyl)perhydroazepine, trifluoracetic acid salt (COMPOUND 574)

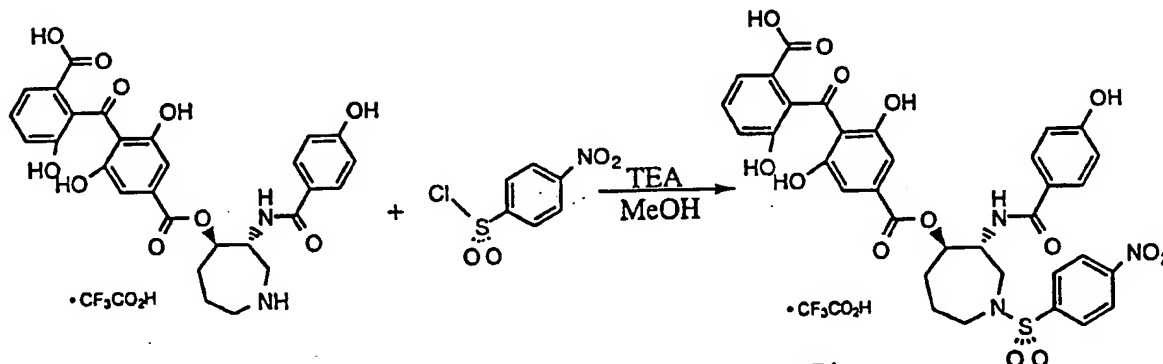
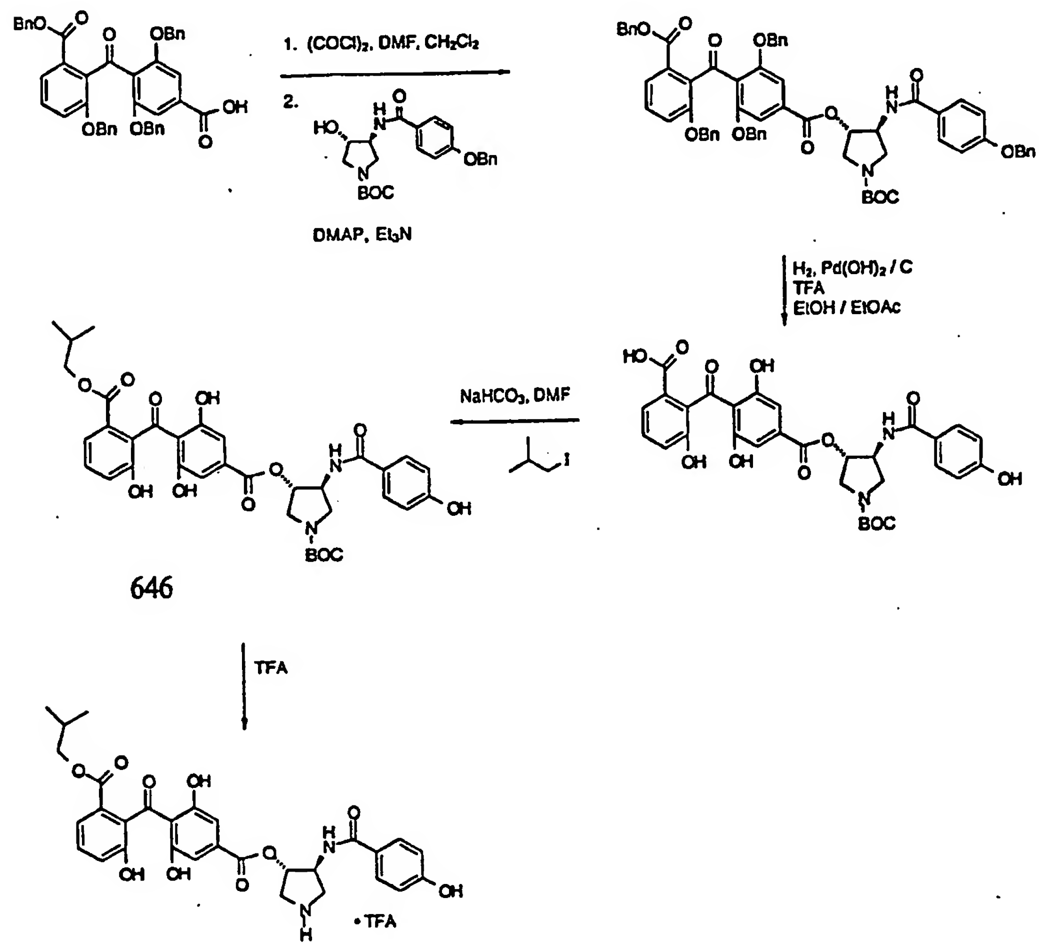


Figure AG

Racemic balanol (preparation described in Compound 508; 100 mg, 147 μmol) was dissolved in methanol (1 ml) and treated with triethylamine (204 μl, 1.47 μmol) and 4-nitrobenzene sulfonyl chloride (48.7 mg, 219.7 μmol) in methylene chloride (1 ml). After stirring at room temperature for 3 h, the mixture was concentrated under vacuum to a yellow film. The residue was dissolved in DMF (2 ml) and chromatographed on a Dynamax-60 C_{18} column (41 mm ID x 25 cm length) using a linear gradient from 100% A (0.1% TFA and 5% acetonitrile in water) to 100% B (pure acetonitrile) over 60 m at 25 ml/min. The clean product, which eluted in 34 m, was freeze-dried to give a yellow powder (12 mg, 11%): m.p. 186-188°C dec; ^{1}H-NMR (DMSO, 300 MHz) δ 1.80-1.97 (3H, m), 2.07-2.18 (1H, m), 3.13 (2H, pseudo t), 4.42-4.53 (1H, m), 5.17-5.28 (1H, m), 6.75 (2H, d, J = 6 Hz), 7.03 (1H, d, J = 8 Hz), 7.19 (1H, d, J = 9 Hz), 7.26 (1H, t), 7.34 (1H, d, J = 8 Hz), 7.63 (1H, d, J = 8 Hz), 7.76 (1H, d, J = 9 Hz); 7.88 (1H, d, J = 9 Hz), 8.15 (2H, d, J = 9 Hz), 8.43 (2H, d, J = 9 Hz),

9.84 (1H, pseudo s, 11.71 (1H, pseudo s); IR (KBr): cm^{-1} 3422, 3273, 3250, 3108, 3081, 2873, 2361, 2339, 1676, 1636, 1606, 1536, 1497, 1426, 1369, 1288, 1232, 1200, 1148, 1093, 1072, 1013, 960, 920, 874, 856, 761, 724, 681, 606, 568. Anal. Calcd. for $C_{34}H_{29}N_3O_{14}S$ ∘ 1 H_2O ∘ 1.2 TFA ∘ .17 CH_3CN: C, 49.17; H, 3.67; N, 4.94; S, 3.57. Found: C, 49.16; H, 3.57; N, 4.64; S, 3.36. LRMS (FAB) m/z 736.1 (735.68 calculated for $C_{34}H_{29}N_3O_{14}S$).

Trans-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-(2-methyl-pr pyloxy)carbonylb nz yl)-3,5-dihydroxyb nzoyloxy]pyrrolidin triflu roacetic acid salt (COMPOUND 577)



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577

Trans-N-t-butoxycarbonyl-3-(4-benzyloxybenzamido)-4-[4-(2-benzyloxy-6-benzyloxycarb nylbenzoyl)-3,5-dibenzyloxy]-pyrrolidine

4-[4-(2-benzyloxy-6-benzyloxycarbonylbenzoyl)]-3,5-dibenzyloxybenzoic acid (1.47 mmol, 996 mg) and 15 ml anhydrous CH_2Cl_2 in a dry round-bottom flask were cooled in an ice/water bath under N_2. To this was added oxalyl chloride (2.87 mmol, 0.25 ml) and 5 drops of DMF. This was allowed to stir for 2 hours while the bath melted. TLC (2:1 hexanes:EtOAc) indicated complete formation of the acid chloride. The solvent was removed in vacuo.

In a 200 ml dry round-bottom flask was added trans-N-t-butoxycarbonyl-3-(4-benzyloxybenzamido)-4-hydroxypyrrolidine (1.26 mmol, 500 mg) in 12 ml anhydrous CH_2Cl_2 under N_2. To this was added triethylamine (3.6 mmol, 0.5 ml) and DMAP (150 mg). A solution of the acid chloride generated above in 10 ml anhydrous CH_2Cl_2 was added via cannula. This was allowed to stir under N_2 at room temperature overnight. The reaction mixture was then diluted with CH_2Cl_2, washed with sat. $NaHCO_3$, brine, then dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified via flash column chromatography using 5% acetone/CH_2Cl_2 as the eluent. Trans-N-t-butoxycarbonyl-3-(4-benzyloxybenzamido)-4-[4-(2-benzyloxy-6-benzyloxycarbonylbenzoyl)-3,5-dibenzyloxy benzoyloxy] pyrrolidine (1.08 mmol, 1.15 g) was obtained in 86% yield.

Trans-N-t-butoxycarbonyl-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-carboxybenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine

To a 500 ml 3-neck round-bottom flask was added trans-N-t-butoxycarbonyl-3-(4-benzyloxybenzamido)-4-[4-(2-benzyloxy-6-benzyloxycarbonylbenzoyl)-3,5-dibenzyloxy benzoyloxy]pyrrolidine (1.02 mmol, 1.08 g) in 17 ml EtOAc and 70 ml ethanol under N_2. To this was added trifluoroacetic acid (2.55 mmol, 0.20 ml) and $Pd(OH)_2/C$ (730 mg) followed immediately by introduction of H_2 at 1 atmosphere. After a reaction time of 3.5 hours, the reaction was flushed with N_2

and filtered through Celite, rinsing with ethanol. Following concentration in vacuo, crude product (644 mg) was obtained in quantitative yield. A small portion was purified via HPLC (21 x 250 mm C18 column, gradient %B = 0 to 50 over 60 min. where A = 0.1% TFA, 5% CH_3CN in water and B = CH_3CN, 15 ml/min. UV = 254 nm) for characterization and the remainder was used crude in subsequent reactions. m.p. 196°C(dec). IR (KBr) 3375(br), 2978, 1704, 1660, 1637, 1607, 1506, 1426, 1368, 1231 cm^{-1}. ^1H NMR CD_3OD, δ 8.52 (d, 1H), 7.72 (d, 2H), 7.49 (d, 1H), 7.26 (t, 1H), 7.01 (d, 1H), 6.91 (s, 2H), 6.80 (d, 2H), 5.40 (m, 1H), 4.63 (m, 1H), 3.87 (m, 2H), 3.50 (m, 2H), 1.47 (s, 9H). LRMS (M + 1) cacld for $C_{31}H_{31}N_2O_{12}$ 623.2, found 623.2. Anal. Calcd for $C_{31}H_{31}N_2O_{12}$ • 1.5 H_2O: C, 57.317; H, 5.120; N, 4.312. Found: C, 57.26; H, 5.18; N, 4.47.

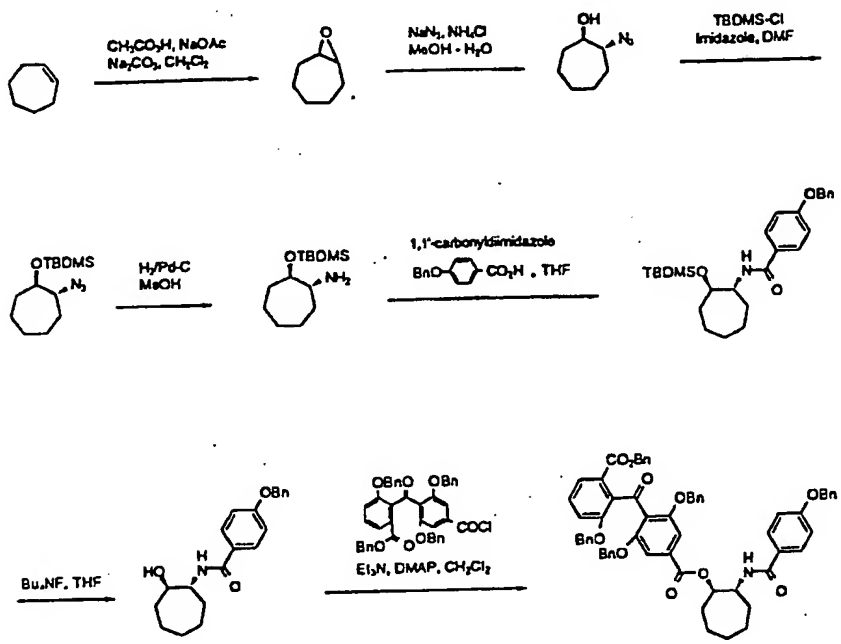
Trans-N-t-butoxycarbonyl-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-(2-methylpropyloxy)carbonylbenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine (COMPOUND 646)

To a round-bottom flask was added trans-N-t-butoxycarbonyl-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-carboxylbenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine (0.15 mmol, 95 mg) in 5 ml DMF. To this was added $NaHCO_3$ (0.23 mmol, 19 mg) and 1-iodo-2-methylpropane (0.75 mmol, 0.09 ml). This was allowed to stir under N_2 for 7 days with additional 1-iodo-2-methylpropane being added each day. A total of 48 additional equivalents (7.2 mmol, 0.83 ml) were added over the reaction period. The reaction mixture was diluted with EtOAc and washed with water 3 times. The aqueous layer was back extracted with EtOAc and the organic layers combined and dried over $MgSO_4$ then concentrated in vacuo. The crude product was purified via HPLC (21 x 250 mm C18 column, gradient %B = 25 to 100 over 60 min. where A = 0.1% TFA, and 5% CH_3CN in water, B = CH_3CN, 15 ml/min. UV = 254 nm) to isolate trans-N-t-butoxycarbonyl-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-(2-methylpropyloxy)-carbonylbenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine (46.5 mg, 44% yield).

Trans-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-(2-methylpr pyloxy)carbonylbenzoyl)-3,5-dihydroxybenzoyloxy]-pyrrolidine trifluoroacetic acid salt (COMPOUND 577)

Trans-N-t-butoxycarbonyl-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-(methylpropyloxy)carbonylbenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine (46.5 mg, 0.068 mmol) was dissolved in 0.75 ml neat trifluoroacetic acid and allowed to stir at room temperature under N_2 for 45 minutes at which time TLC (75% CH_2Cl_2, 24% MeOH, 1% (10% aq.) NH_4OH) indicated the reaction was complete. This was diluted with toluene and concentrated in vacuo to yield 42.7 mg (91% yield) of crude product. Purification via HPLC (21 x 250 mm C18 column, gradient %B = 0 to 100 over 60 min. where A = 0.1% TFA, 5% CH_3CN in water, B = CH_3CN, 15 ml/min. UV = 254 nm) yielded trans-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-(2-methylpropyloxy)-carbonylbenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine trifluoroacetic acid salt (Compound 577, 32 mg, 68% yield) as a yellow solid. m.p. 150-156°C (dec.). IR (KBr) 3191 (br), 2968, 1677, 1607, 1508, 1426, 1373, 1293, 1201 cm-1. 1H NMR, DMSO-d_6, δ, 11.74 (s, 2H), 10.13 (s, 1H), 10.03 (s, 1H), 9.20 (br, NH), 8.51 (d, 1H), 7.74 (d, 2H), 7.44 (d, 1H), 7.35 (t, 1H), 7.12 (d, 1H), 6.95 (s, 2H), 6.84 (d, 2H), 5.50 (m, 1H), 4.60 (m, 1H), 3.88 (d, 2H), 3.72 (m, 2H), 3.52 (m, 2H), 1.80 (q, 1H), 0.83 (d, 6H). LRMS (M + 1) calcd for $C_{30}H_{31}N_2O_{10}$ 579.20, found 579.1. Anal. calcd for $C_{30}H_{30}N_2O_{10} \circ C_2HF_3O_2 \circ 1.3\ H_2O$: C, 53.68; H, 4.73; N, 3.91. Found: C, 53.78; H, 4.54; N, 3.99.

Trans-1-(4-hydroxyb nzamido)-2-[4-(2-hydr xy-6-hydroxycarbonylbenzoyl)-3,5-dihydroxybenzoyl xyl]cycloheptane (COMPOUND 588)



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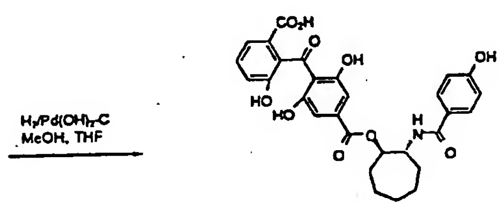


588

NaOAc (426 mg, 5.2 mmol) was dissolved in a solution of peroxyacetic acid in acetic acid (32 wt. %, 21.9 ml, 104 mmol) and the resultant solution was added dropwise over 30 min. to a mixture of cycloheptene (10 g, 104 mmol) and Na_2CO_3 (44.1 g, 416 mmol) in CH_2Cl_2 (100 ml) at 5°C. The mixture was allowed to stir at room temperature for 3h with occasional cooling using a water bath. All solid material was removed by filtration, and the filtrate was distilled at atmospheric pressure using a vigreux column to remove most of the CH_2Cl_2, giving a colorless liquid which was shown by H^1 NMR to be a mixture of the epoxide and CH_2Cl_2. The purity was estimated to be ca. 73% in the epoxide (total 15.93 g, 100% crude yield). This material was used without further purification in the next step.

A mixture of the epoxide from the previous step (10 g, 65 mmol), NaN_3 (27.5 g, 423 mmol), NH_4Cl (10.44 g, 195 mmol), MeOH (162 ml), and H_2O (20 ml) was stirred at reflux for 24h. The solid was removed by filtration and the filtrate was evaporated. The residue was treated with 0.5 N aq. NaOH (50 ml) and extracted with CH_2Cl_2 (3 x 30 ml). The combined CH_2Cl_2 extracts were washed with H_2O (50 ml), brine (50 ml), dried ($MgSO_4$), and evaporated to give the azide (8.39 g, 83%).

The azide (7 g, 45 mmol) in N,N-dimethylformamide (10 ml) was added to a solution of t-butyldimethylsilylchloride (6.8 g, 45 mmol) and imidazole (3.07 g, 45 mmol) in N,N-dimethylformamide (35 ml). The resultant mixture was stirred at room temperature for 16h, diluted with Et_2O (70 ml), washed with H_2O (4 x 30 ml) and brine (50 ml), dried ($MgSO_4$), and evaporated to give a pale yellow oil (11.33 g, 93%).

A mixture of the product of the previous reaction (8.1 g, 29.95 mmol) and 5% Pd on carbon (1.59 g, 2.5 mol. %) in MeOH was stirred vigorously under 1 atm H_2 at room temperature for 20h. The catalyst was removed by filtration over Celite and the filtrate was evaporated. The residue was purified by flash chromatography (SiO2, Et_2O: Hexane = 2:1) to give the amine as a colorless oil (5.27 g, 72%).

A mixture of 4-benzyloxybenzoic acid (3.287 g; 14.40 mmol) and 1,1'-carbonyldiimidazole (2.335 g, 14.40 mmol) in THF was stirred at room temperature for 2h. To the resultant slurry was added a solution of the amine product of the previous reaction (3.07 g, 12.56 mmol) in THF and stirring was continued at room temperature for 24h. The mixture was diluted with CH_2Cl_2 (40 ml), washed with H_2O (3 x 15 ml) and brine (2 x 15 ml), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (SiO_2, Et_2O : hexane = 1:5) to give the amide as a white powder (4.69 g, 82%).

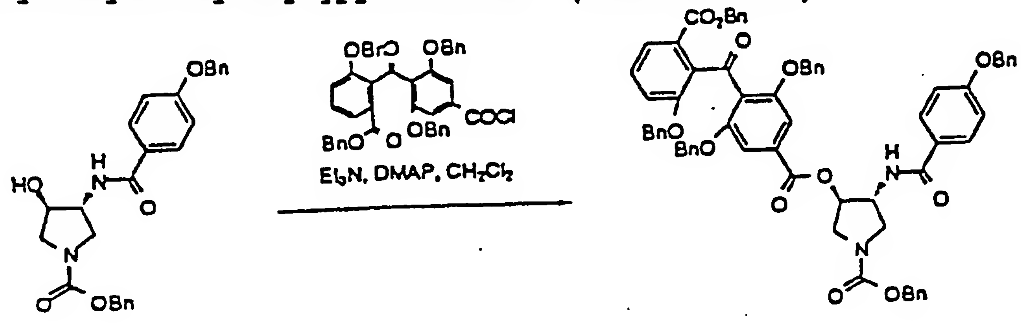
Tetrabutylammonium fluoride in THF (1M, 10 ml, 10 mmol) was added to a solution of the amide product from the previous reaction (3.8 g, 8.36 mmol) in THF and the resultant yellow solution was stirred at room temperature for 2h. The mixture was poured into CH_2Cl_2 (150 ml), washed with H_2O (3 x 30 ml) and brine (2 x 30 ml), dried ($MgSO_4$), and concentrated to about 30 ml. The precipitate was collected by filtration and washed with CH_2Cl_2 (3 x 3 ml). The combined filtrate and washes were concentrated to about 10 ml, and the resultant precipitate was collected, washed with CH_2Cl_2 (2 x 2 ml), combined with the first crop and dried under vacuum. This gave a white solid (2.24 g, 79%). The mother liquors were combined and chromatographed (SiO_2, Et_2O : hexane = 1:5 followed by CH_2Cl_2 to give an additional 256 mg of the product, total yield: 89%.

To a stirred solution of 4-(2-benzyloxycarbonyl-6-benzyloxy)benzoyl-3,5-dibenzyloxybenzoylchloride (350 mg, 0.52 mmol) in CH_2Cl_2 (1.5 ml) was added oxalyl chloride (0.067 ml, 0.77 mmol) and one drop of N,N-dimethylformamide. The resultant solution was stirred at room temperature for 2h and then evaporated to dryness. The residue was dissolved in CH_2Cl_2 (1 ml) and added to a mixture of the product of the preceding reaction (177 mg, 0.52 mmol) and Et_3N (105 mg, 1.04 mmol) in CH_2Cl_2 (2 ml). The mixture was stirred at room temperature for 17h, diluted with CH_2Cl_2 (15 ml), washed with H_2O (3 x 10 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed

(SiO_2, Et_2O: hexane = 1:1, followed by Et_2O: hexane: CH_2Cl_2 = 1:1:1) to give a white solid (166 mg, 32%).

$Pd(OH)_2$ on carbon (20 wt. % contains ≥ 50% moisture; 22 mg, 0.016 mmol) and MeOH (1.6 ml) were added to a solution of the product of the preceding reaction (160 mg, 0.16 mmol) in THF (1.6 ml) and the resultant mixture was stirred under 1 atm H_2 at room temperature for 17h. The catalyst was removed by filtration over Celite and the Celite pad was washed with MeOH (15 ml). The filtrate and washes were combined and evaporated to give a yellow solid (83 mg, 95%) (COMPOUND 588). m.p. 186°C (dec). Anal. calcd for $C_{29}H_{27}NO_{10}\cdot 1H_2O$: C, 61.37; H, 5.15; N, 2.47. Found: C, 61.41; H, 5.29; N, 2.36.

Trans-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-hydroxycarbonyl b nzoyl)-3,5-dihydroxybenzoyloxyl]pyrrolidinium trifluor acetate (COMPOUND 589) and 1-Hexadecanoyl-trans-3-(4-hydroxybenzamido)-4-[40(2-hydroxy-6-hydroxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxyl]pyrrolidine (COMPOUND 590)



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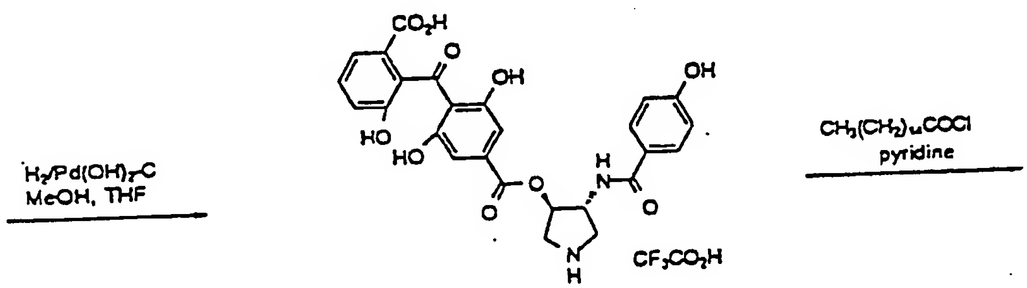

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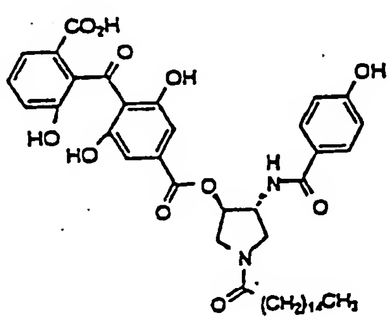


590

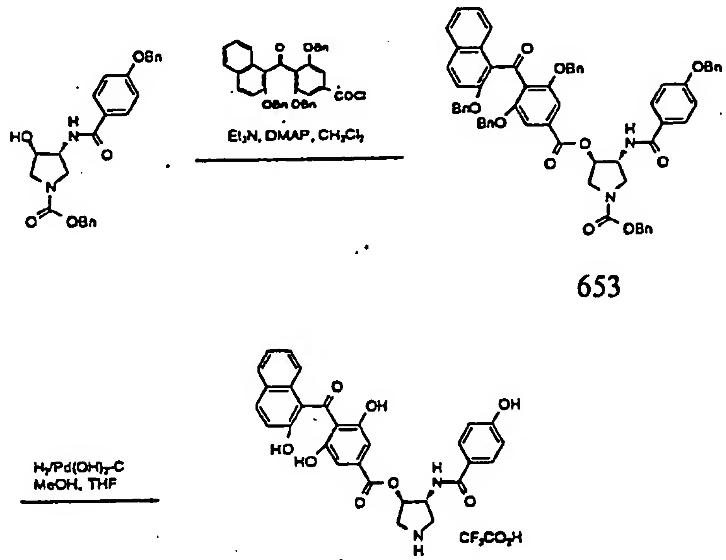
To a stirred solution of 4(2-benzyloxycarbonyl-6-benzyloxy)benzyl-3,5-dibenzyloxybenzoylchloride (350 mg, 0.52 mmol) in CH_2Cl_2 (1.5 ml) was added oxalyl chloride (0.067 ml,

0.77 mmol) and one drop of N,N-dimethylformamide. The resultant solution was stirred at room temperature for 2h and then evaporated to dryness. The residue was dissolved in CH_2Cl_2 (1.5 ml) and added to a mixture of trans-3-(4-hydroxy-1-benzyloxycarbonyl pyrrolidine (232 mg, 0.53 mmol; for preparation see Compound 585), Et_3N (0.14 ml, 1.04 mmol), and 4-(N,N-dimethylamino)pyridine (6 mg, 0.052 mmol) in CH_2Cl_2 (1.5 ml). The mixture was stirred at room temperature for 17h, diluted with CH_2Cl_2 (15 ml), washed with H_2O (3 x 10 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2, Et_2O:hexane = 1:1, then Et_2O:hexane:CH_2Cl_2 = 1:1:0.5) to give the ester (230 mg, 40%) (COMPOUND 652).

To a solution of Compound 652 (200 mg, 0.18 mmol) in THF (1.8 ml) were added MeOH (1.8 ml), $Pd(OH)_2$ on carbon (20 wt.%, contains ≥ 50% moist; 25 mg, 0.018 mmol), and CF_3CO_2H (41 mg, 0.36 mmol). The mixture was stirred at room temperature under 1 atm H_2 for 17h. The volatile components were removed by evaporation, and the residue was taken up in MeOH, filtered through Celite, and evaporated to give a yellow solid (88 mg, 72%) (COMPOUND 589).

Palmitoyl chloride (10 mg, 0.038 mmol) was added to a stirred solution of Compound 589 (24 mg, 0.038 mmol) in pyridine (0.4 ml). The mixture was stirred at room temperature for 16h and TLC showed that the reaction was incomplete. More palmitoyl chloride (5 mg) was added and stirring was continued for 16h. The reaction mixture was evaporated to remove pyridine leaving a yellow syrup with some solid material which was shown to contain starting material by ^1H NMR. This material was dissolved in pyridine (0.4 ml) and treated with palmitoyl chloride (15 mg). The mixture was stirred at room temperature for 24h, evaporated, and chromatographed (SiO_2, EtOAc followed by 5% HOAc in acetone) to give a yellow solid (19 mg, 66%) which was shown by ^1H NMR to be the desired amide (Compound 590) with some contamination. m.p. 175-178°C (dec). Anal. calcd for $C_{42}H_{52}N_2O_{11}\cdot 3H_2O$: C, 61.90; H, 7.17; N, 3.44. Found: C, 61.85; H, 7.07; N, 3.62.

Trans-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-naphth-1-oyl)-3,5-dihybroxybenzyoyloxyl]pyrrolidine trifluoroacetic acid salt (COMPOUND 591)



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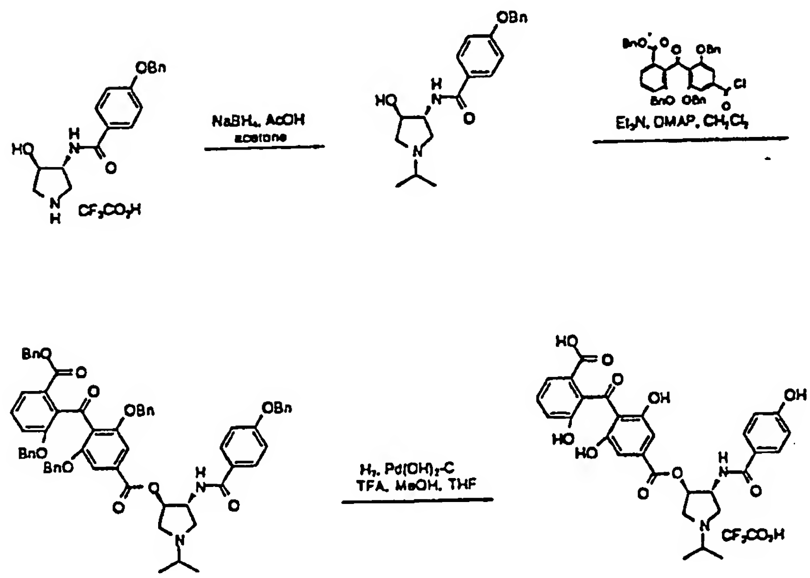
591

To a mixture of 4-(2-benzyloxy-naphth-1-oyl)-3,5-dibenzyloxylbenzoic acid (297 mg, 0.5 mmol) and 2 drops of N,N-dimethylformamide in CH_2Cl_2 (1.5 ml) was added oxalyl chloride (0.065 ml, 0.75 mmol) dropwise over 2 min. The resultant mixture was stirred at room temperature for 2h and the volatile components were evaporated. The remaining yellow solid was dried under vacuum for 1h, dissolved in CH_2Cl_2 (1.5 ml), and added to a solution of trans-3-(4-hydroxybenzamido-4-hydroxy-1-benzyloxycarbonyl pyrrolidine (168 mg, 0.38 mmol; for preparation see Compound 585), Et_3N (0.1 ml, 0.76 mmol), and 4-(N,N-dimethylamino)pyridine (5 mg, 0.038 mmol) in CH_2Cl_2 at 5°C.

The mixture was stirred at room temperature for 16h, diluted with CH_2Cl_2 (10 ml), washed with H_2O (3 x 10 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2, Et_2O:hexane = 1:1, followed by Et_2O:hexane:CH_2Cl_2 = 1:1:0.5) to give a white solid (336 mg, 66%) (COMPOUND 653).

$Pd(OH)_2$ on carbon (20 wt.%, contains ≥ 50% moist; 21 mg, 0.015 mmol), followed by CF_3CO_2H (34 mg, 0.3 mmol) and MeOH (1.5 ml), was added to a solution of Compound 653 (155 mg, 0.15 mmol) in THF (1.5 ml). The resultant mixture was stirred at room temperature under 1 atm H_2 for 20h. The catalyst was removed by filtration over Celite and the Celite pad was washed with MeOH (20 ml). The combined filtrate and washes were evaporated to give a yellow solid (85 mg, 88%) (COMPOUND 591).

1-Isopr pyl-trans-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-hydroxycarb nylbenzoyl)-3,5-dihydroxybenzoyloxyl]pyrrolidinium trifluoroacetate (COMPOUND 592)



654

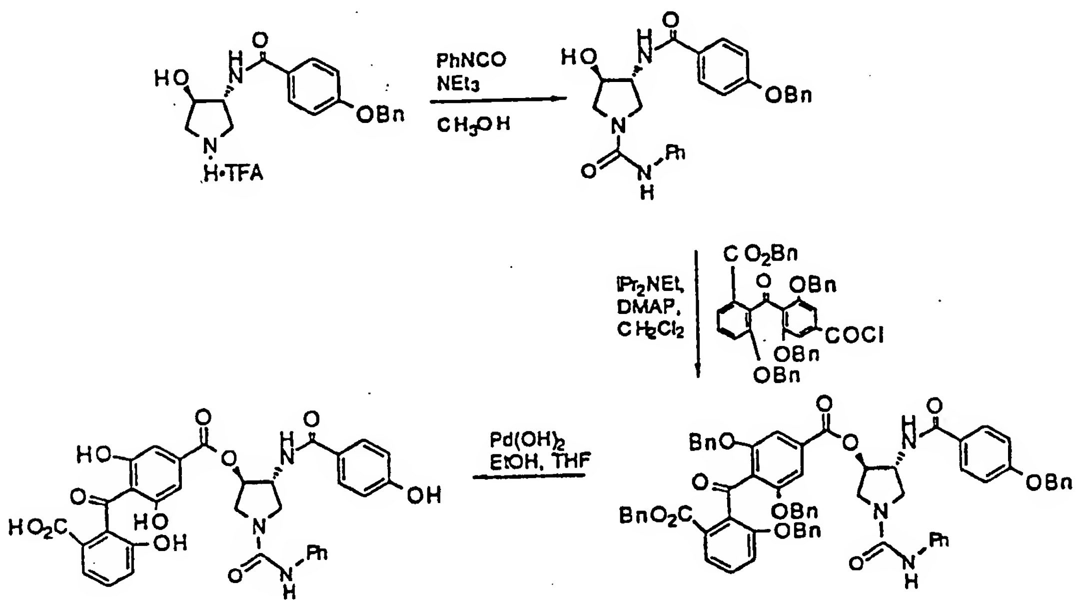
592

To a solution of trans-3-(4-benzyloxybenzamido)-3-hydroxy pyrrolidine (213 mg, 0.5 mmol) in acetic acid (2.5 ml) was added $NaBH_4$ (95 mg, 2.5 mmol) in small portions. After the H_2 evolution had ceased (ca. 10 min.) acetone (0.18 ml, 2.5 mmol) was added and the mixture was stirred at room temperature for 16h. The reaction mixture was basified with 2N KOH and the resultant cloudy mixture was extracted with CH_2Cl_2 (3 x 15 ml). The combined CH_2Cl_2 extracts were dried ($MgSO_4$), and evaporated to give a colorless oil (163 mg, 92%).

Oxalyl chloride in CH_2Cl_2 (2 M, 0.39 ml, 0.78 mmol) was added dropwise to a solution of 4-(2-benzyloxy-6-benzyloxycarbonylbenzoyl)-3,5-dibenzyloxybenzoic acid (353 mg, 0.52 mmol) and a drop of DMF in CH_2Cl_2 (2 ml) at 5°C. The mixture was stirred at room temperature for 2h, then evaporated to remove the solvent and excess oxalyl chloride. The residue was dried *in vacuo* for 1h, dissolved in CH_2Cl_2 (1 ml), and added to a mixture of the product of the preceding reaction (142 mg, 0.4 mmol), Et_3N (81 mg, 0.8 mmol), and DMAP (6 mg, 0.054 mmol) in CH_2Cl_2 (2 ml) at 5°C. The mixture was stirred at room temperature for 17h, diluted with CH_2Cl_2 (15 ml), washed with H_2O (3 x 10 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2, Et_2O:CH_2Cl_2:hexane = 1:1:1 followed by Et_2O:CH_2Cl_2:hexane = 2:2:1) to give a pale yellow oil (82 mg, 20%) (COMPOUND 654).

$Pd(OH)_2$ on carbon(20 wt%, contains <50% moist, 11 mg, 0.008 mmol), trifluoroacetic acid (18 mg, 0.16 mmol), and MeOH (1 ml) was added to a solution of Compound 654 (84 mg, 0.08 mmol) in EtOAc (1 ml) and the mixture was stirred under 1 atm H_2 contained in a balloon at room temperature for 16h. The mixture was filtered through Celite and the Celite pad was washed with MeOH (5 ml). The combined filtrates were evaporated to give a yellow solid (32 mg, 59%) (COMPOUND 592). IR (KBr, cm^{-1}):1705, 1676, 1636, 1607. FBMS: M/Z = 565 (M + 1).

(±)-Trans-4-[4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)-1-[(phenylamin)carbonyl]-pyrrolidine (COMPOUND 593)



593

655

(±)-Trans-4-Hydroxy-3-(4-benzyloxybenzamido)-1-[phenylamino)carbonyl]-pyrrolidine

To a solution of (±) trans-4-hydroxy-3-(4-benzyloxybenzamido pyrrolidine • TFA (100 mg, 0.235 mmol) in methanol (4.7 ml) were added triethyl amine (66 µL, 0.470 mmol, 2.0 eq) then phenyl isocyanate (26 µL, 0.235 mmol, 1.0 eq). The cloudy mixture was stirred at room temperature under N_2 45 min, then poured into H_2O (30 ml) and extracted with CH_2Cl_2 (3 x 25 ml). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated to a white solid (82 mg, 81%): ^1H NMR (300 MNz, CD_3OD δ 7.60 (d, J = 8.8 Hz, 2H), 7.00-7.25 (m, 11H), 6.85 (d, J = 8.9 Hz, 2H), 6.79 (d, J = 7.1 Hz, 1H), 4.93 (s, 2H), 4.20-4.25 (m, 1H), 4.16 (dd, J = 8.2, 3.1 Hz, 1H), 3.73

(dd, J = 11, 6.4 Hz, 1H), 3.57 (dd, J = 11.4, 5.1 Hz, 1H), 3.12 (dd, J = 11.0, 3.5 Hz, 1H), 3.26 (dd, J = 11.1, 2.8 Hz, 1H).

(±)-Trans-4-[4-(6-benzyloxy-2-(benzyloxycarbonyl)benzoyl]-3,5-dibenzyloxybenzoyloxy)-3-(4-benzyloxybenzamido)-1-[(phenylamino)carbonyl]-pyrrolidine (COMPOUND 655)

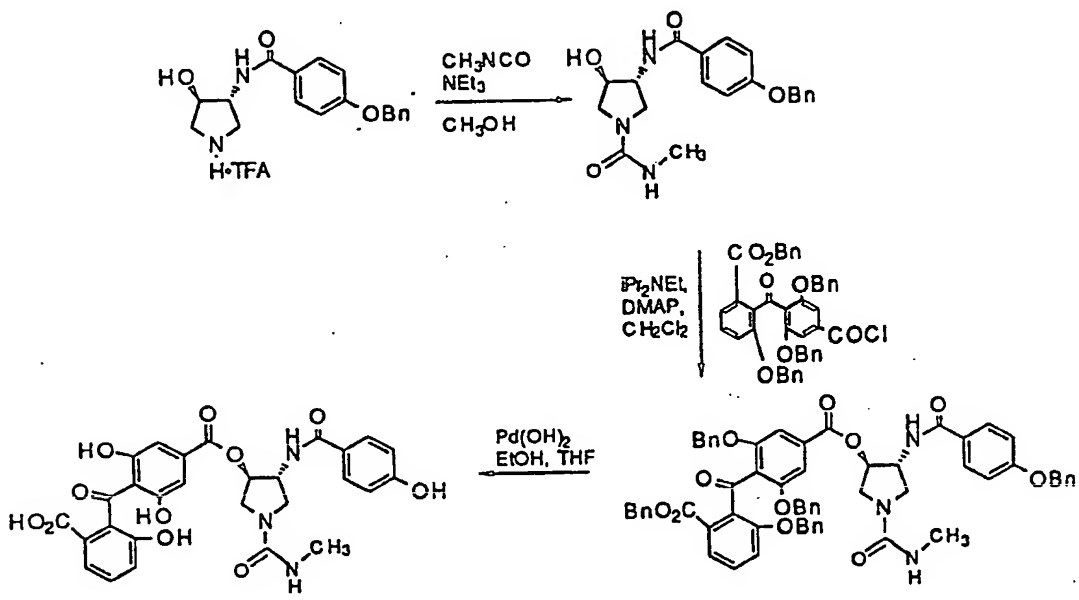
To a solution of the product of the preceding reaction (80 mg, 0.19 mmol), 4-dimethylaminopyridine (26 mg, 0.21 mmol, 1.1 eq) and diisopropylethylamine (37 μL, 0.21 mmol, 1.1 eq) in CH_2Cl_2 (3.2 ml) was added a solution of acid chloride (0.21 mmol) in CH_2Cl_2 (1.6 ml). The mixture was stirred at room temperature under N_2 18 h, then poured into 5% HCl (30 ml) and extracted with CH_2Cl_2 (3 x 25 ml). The organic layers were combined, dried ($MgSO_4$) filtered and evaporated. Flash column chromatography of the golden residue (1.1 hexanes:ethyl acetate) on silica gel provided the title product (110 mg, 53%) as an off white foam: ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 8.8 Hz, 2H), 6.9-7.6 (m, 26H), 6.82 (d, J = 7.5 Hz, 2H), 5.4-5.5 (m, 1H), 5.12 (s, 2H), 5.02 (s, 2H), 4.80 (m, 1H), 4.76 (s, 4H), 4.68 (s, 2H), 4.0-4.05 (m, 1H), 3.95-4.0 (m, 1H), 3.65-3.7 (m, 1H), 3.6-3.65 (m, 1H).

(±)-Trans-4-[4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)-1-[(phenylamino)carbonyl]-pyrrolidine (COMPOUND 593)

To a round bottom flask containing Compound 655 (110 mg, 0.101 mmol) were added $Pd(OH)_2$ (22 mg of a 20% powder) then THF (2.2 ml) and ethanol (2.2 ml). The flask was evacuated and filled with H_2 twice, then allowed to stir under H_2 (1 atm) for 23 h. The suspension was filtered, washed through with methanol (40 ml) and evaporated to a yellow solid. Purification by reverse phase HPLC (618 column) provided the title product as a yellow powder after lyophilization (24.9 mg, 39%): m.p. 183-208° (dec); IR (KBr) 3458, 3336, 1719, 1679, 1622, 1227, 760 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.53 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 7.7 Hz, 1H), 7.20 (d, J = 7,7 Hz, 2H), 7.0-7.1 (m, 3H), 6.82 (d, J = 8.3 Hz, 2H), 6.73 (s, 2H), 6.62

(8.7, J = d Hz, 2H), 5.25-5.35 (m, 1H), 4.5-4.6 (m, 1H), 3.75-3.9 (m, 2H), 3.4-3.5 (m, 2H); MS *m/e* calc'd for $C_{33}H_{28}N_3O_{11}$: 642.1732, found 642.1865; Analysis calc'd for $C_{33}H_{27}N_3O_{11}\cdot0.5$ TFA•1.25 H_2O: C,56.63; H, 4.19; N, 5.83; found: C, 56.85; H, 4.26; N, 5.96.

(±) Trans-4[4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)-1-[(methylamino)carb nyl]-pyrrolidine (COMPOUND 594)



594 656

(±)-Trans-4-Hydroxy-3-(4-benzyloxybenzamido)-1-[(methylamino)carbonyl]-pyrrolidine

To a solution of (±)-trans-4-hydroxy-3-(4-benzyloxybenzamido)pyrrolidine • TFA (100 mg, 0.235 mmol) in methanol (4.7 ml) were added triethyl amine (66 μl, 0.470 mmol, 2.0 eq) then methyl isocyanate (14 μL, 0.235 mmol, 1.0 eq). The cloudy mixture was stirred at room temperature under N_2 1.5 h, then more methyl isocyanate (14 μL, 1.0 eq) was added. The mixture was allowed to stir 10 min more, then poured into H_2O (30 ml) and extracted with CH_2Cl_2 (3 x 25 ml). The organic layers were combined, dried ($MgSO_4$) filtered and evaporated to

a white solid (83 mg, 95%): ^{1}H NMR (300 MHz, CD_3OD) δ 7.60 (d, J = 8.8 Hz, 2H), 7.1-7.25 (m, 5M), 6.85 (d, J = 8.8 Hz, 2H), 4.66 (s, 2H), 4.15 (dd, J = 6.5, 3.4 Hz, 1H), 4.10 (dd, J = 5.0, 3.4 Hz, 1H), 3.57 (dd, J = 10.8, 6.5 Hz, 1H), 3.43 (dd, J = 11.1, 5.2 Hz, 1H), 3.1-3.2 (m, 2H), 2.53 (s, 3H).

(±)-Trans-4-[4-(6-benzyloxy-2-(benzyloxycarbonyl)benzoyl]-3,5-dibenzyloxybenzoyloxy)-3-(4-benzyloxybenzamido)-1-[(methylamino)carbonyl]-pyrrolidine (COMPOUND 656)

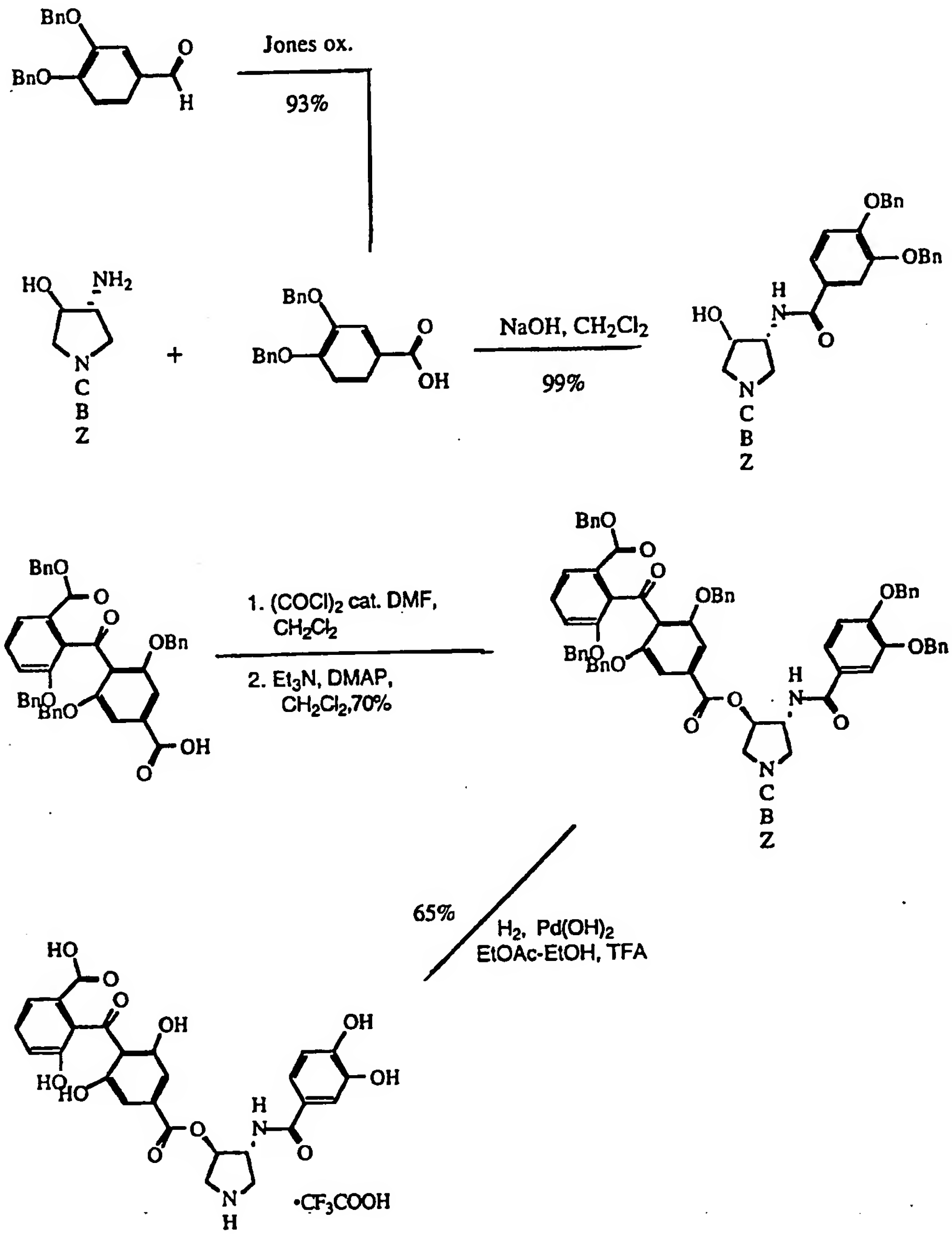
To a solution of the product of the prececeding reaction (85 mg, 0.23 mmol), 4-dimethylaminopyridine (28 mg, 0.23 mmol, 1.1 eq) and diisopropylethylamine (40 µL, 0.23 mmol, 1.1 eq) in CH_2Cl_2 (3.9 ml) was added a solution of acid chloride (0.25 mmol) in CH_2Cl_2 (1.9 ml). The mixture was stirred at room temperature under N_2 16 h, then poured into 5% HCl (30 ml) and extracted with CH_2Cl_2 (3 x 25 ml). The organic layers were combined, dried ($MgSO_4$) filtered and evaporated. Flash column chromatography of the golden residue (98:2 CH_2Cl_2:methanol) on silica gel provided the title product (159 mg, 67%) as an off white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 8.7 Hz, 2H), 7.3-7.4 (m, 5H), 7.1-7.3 (m, 16H), 7.06-7.08 (m, 6H), 6.9-7.0 (m, 3H), 6.84 (d, J = 7.6 Hz, 2H), 5.49 (m, 1H), 5.14 (s, 2H), 5.07 (s, 2H), 4.78 (s, 4H), 4.70 (m, 1H), 4.70 (s, 2H), 4.40 (m, 1H), 3.95-4.0 (m, 2H), 3.53-3.60 (m, 2H), 2.80 (d, J = 4.5 Hz, 3H).

(±)-Trans-4-[4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxyenzoyloxy]-3-(4-hydroxybenzamido)-1-[(methylamino)carbonyl]-pyrrolidine (COMPOUND 594)

To a round bottom flask containing Compound 656 (159 mg, 0.154 mmol) were added $Pd(OH)_2$ (40 mg of a 20% powder) then THF (3.0 ml) and ethanol (3.0 ml). The flask was evacuated and filled with H_2 twice, then allowed to stir under H_2 (1 atm) for 21 h. The suspension was filtered, washed through with methanol (50 ml) and evaporated to a yellow solid. Purification by reverse phase HPLC (C18 column) provided the title product as a yellow powder after lyophilization (68.7 mg,

77%): m.p. 178-198° (dec); IR (KBr) 3385, 1714, 1605, 1236, 763 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.53 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 7,7 Hz, 1H), 7.06 (dd, J = 8.1, 7.9 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 6.70 (s, 2H), 6.62 (d, J = 8.7 Hz, 2H), 5.2-5.3 (m, 1H), 4.4-4.5 (m, 1H), 3.6-3.8(6 line mult, 2H), 3.2-3.4 (m, 2H), 2.53 (s, 3H); MS *m/e* calc'd for $C_{28}H_{25}N_3O_{11}$: 580.1567, found 580.1481; Analysis calc'd for $C_{28}H_{25}N_3O_{11}\circ 0.3TFA\circ 0.8H_2O$: C, 54.32; H, 3.96; N, 6.72; found: C, 54.61; H, 4.32; N, 6.68.

(+)-trans-3-(3,4-dihydroxybenzamido)-4-[4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxy]benzoyloxypyrrolidine trifluoroacetic acid salt (COMPOUND 675)



675

Jones reagent (6ml) was added to a solution of 3,4-dibenzyloxybenzaldehyde (Aldrich, 1.0 g, 3.14 mmol) in acetone (20 ml) until the reaction remained the color of Jones reagent. The excess of Jones reagent was destroyed by adding i-PrOH and acetone was removed in vacuo. The slurry residue was taken into EtOAc, washed with brine, dried with Na_2SO_4, and concentrated to afford off-white solids (0.98 g, 93%).

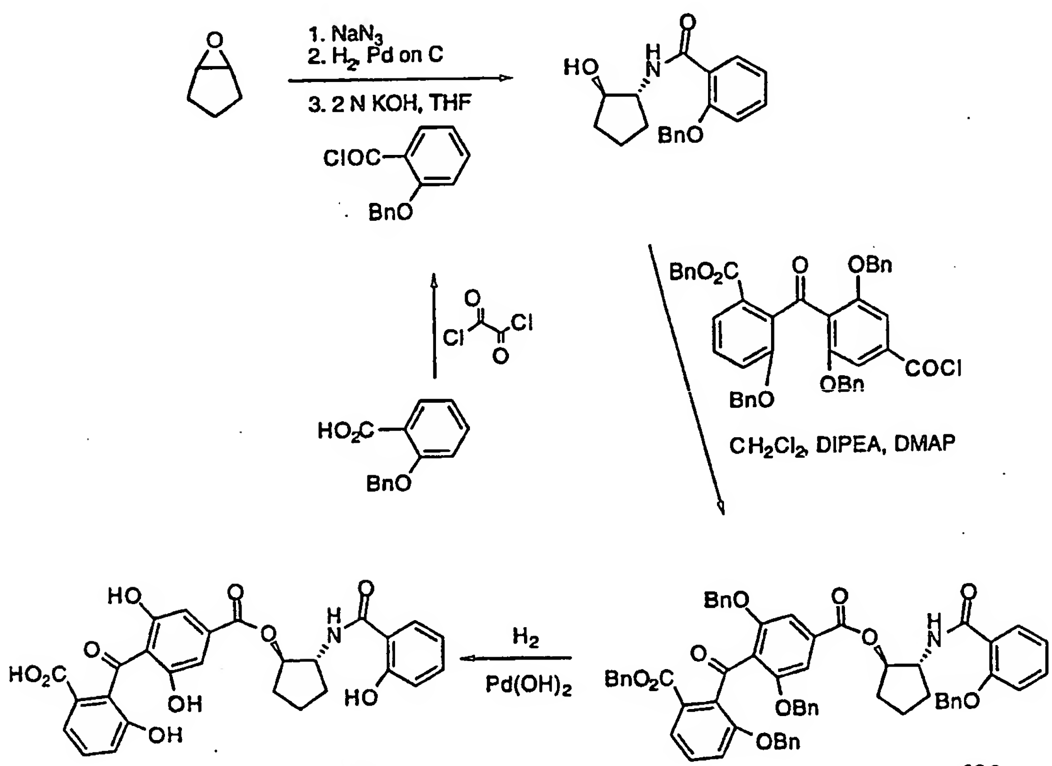
To a suspension of 3,4-dibenzyloxybenzoic acid (0.467 mg, 1.40 mmol) in anhydrous CH_2Cl_2 (5 ml) was added cat. DMF and oxalyl chloride (2.0 M solution in CH_2Cl_2, 1.92 ml, 3.85 mmol) at room temperature The mixture was kept for stirring at room temperature for 2 hr. Solvents were removed and the acid chloride residue was taken into CH_2Cl_2 (5 ml) after drying over the vacuum for 1hr. To a biphasic reaction mixture of N-CBZ-3-amino-4-hydroxypyrrolidine (0.74 M solution in CH_2Cl_2, 300 mg, 1.7 ml, 1.27 mmol) in CH_2Cl_2 (10 ml) and 1 N NaOH (13.0 ml) was added a solution of 3-benzyloxybenzoic acid chloride in anhydrous CH_2Cl_2 (5 ml). The resulting mixture was vigorously stirred at room temperature for 3h. The reaction mixture was diluted with EtOAc, washed with brine, and dried over Na_2SO_4. The crude product after concentration was triturated in Et_2O and EtOAc to afford white solids (quantitative yield).

To a solution of benzophenone acid (265 mg, 0.39 mmol) in CH_2Cl_2 (5 ml) was added cat. DMF and oxalyl chloride (2.0 M solution in CH_2Cl_2, 0.488 ml, 0.976 mmol) at room temperature The mixture was kept for stirring at room temperature for 2 hr. Solvents were removed and the acid chloride residue was taken into CH_2Cl_2 (5 ml) after drying over the vacuum for 1hr.

A solution of amidoalcohol (215.5 mg, 0.39 mmol), Et_3N (197.3 mg, 272 μL, 1.95 mmol) and DMAP (47.6 mg, 0.39 mmol) in CH_2Cl_2 (5 ml) was treated with the freshly made acid chloride-CH_2Cl_2 solution (5 ml) at 5°C. The reaction mixture was allowed to stir at room temperature for 3h and then chromatographed on silica gel eluting with 2:3 to 1:1/EtOAc:Hexane. The product was obtained as fluffy white solids (332 mg, 70%).

The product of the previous reaction (320 mg, 0.264 mmol) was dissolved in EtOAc-HOEt (1:1, 25 ml) and treated with TFA (cat.) followed by 10% $Pd(OH)_2$ (170 mg, 60 mol%). The mixture was subject to hydrogenolysis at 50 psi for 20hr. Solvents were concentrated after filtering through a pad of celite, and the residue was dissolved in DMF (1.0 ml) and loaded onto HPLC; conditions: A-0.1% TFA 5%CH_3CN/H_2O, B-100% CH_3CN, 0-50% B over 60 min, 25 ml/min, 41 x 300 mm C18 column. Fractions (one/min) 37-40 were combined, partially concentrated, and lyophilized to afford fluffy yellow solids (113, 65%). (COMPOUND 675) m.p. 210-213 (dec)°C. IR (KBr) cm^{-1} 3391, 3246, 1717, 1676, 1636, and 1603. Anal. Calcd. for $C_{26}H_{22}N_2O_{11}\bullet 2.0H_2O\bullet 1.0C_2HF_3O_2$: C, 48.84; H, 3.95; N, 4.07. Found: C, 48.75; H, 3.63; N, 4.07. LRFAB (M + 1): 579.

(±)-Trans-2-[4-(6-hydroxy-2-(carboxyl)benzoyl)-3,5-dihydroxybenzoyloxy]-1-(2-hydroxybenzamido)cyclopentane (COMPOUND 681)



681 680

FIGURE AP

(2-Benzyloxybenzoyl)chloride

To a solution of 2-benzyloxybenzoic acid (684 mg, 3.00 mmol) in CH_2Cl_2 (15 ml) were added dimethylformamide (1 drop) then oxalyl chloride (3.0 ml of a 2.0 M solution in CH_2Cl_2, 6.00 mmol, 2.0 eq). The solution was stirred at room temperature 1 h, then evaporated and the light yellow semi-solid was placed on the vacuum pump before use.

(±)-Trans-2-[(2-Benzyloxy)benzamido]hydroxycyclopentane

To a solution of cyclopentene oxide (262 ml, 3.00 mmol) in methanol (5.1 ml) and H_2O (0.9 ml) were added NH_4Cl (161 mg, 3.0 mmol, 1.0 eq) then NaN_3 (390 mg, 6.0 mmol, 2.0 eq). The solution was stirred at 45-50°C under N_2 for 23 h, then allowed to cool. The mixture was diluted with H_2O (10 ml) and extracted with CH_2Cl_2 (4 x 20 ml). The organic layers were dried ($MgSO_4$), filtered and evaporated to a very light yellow oil (not put on vacuum pump) which was used crude for the reduction.

To a solution of the crude azido alcohol from above in methanol (15 ml) was added 10% Pd on C (38 mg). The flask was evacuated and filled with H_2 twice then allowed to stir under H_2 (1 atm) for 1 h. Trifluoroacetic acid (231 L, 1.0 eq) was added, and the mixture stirred under H_2 1 h more. The slurry was filtered through Celite, evaporated, and evaporated from CH_2Cl_2 (30 ml) to remove any remaining methanol.

The resulting amino alcohol was dissolved in THF (2 ml) and 2N KOH (1.5 ml), then a solution of 2-benzyloxybenzoyl chloride (3.00 mmol) in THF (7.0 ml) was added. The mixture was allowed to stir 17 h, then poured into 5% HCl (50 ml) and extracted with CH_2Cl_2 (2 x 50 ml). The organic layers were dried ($MgSO_4$), filtered and evaporated to a tan oil. Flash column chromatography on silica gel (1:3 hexanes:ethyl acetate) provided the title amide alcohol (0.31 g, 33% over 3 steps) as a white powder: ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, J = 7.8 Hz, 1H), 8.18 (bs, 1H), 7.4-7.5 (m, 5H), 7.13 (d, J = 7.6 Hz, 1H), 7.09 (d, J = 8.3 Hz, 1H), 5.14 (s, 2H), 4.7-4.9 (bs, 1H), 3.85-4.0 (m, 2H), 1.8-2.0 (m, 2H), 1.55-1.75 (m, 2H), 1.4-1.55 (m, 1H), 0.9-1.0 (m, 1H).

(±)-Trans-2-[4-(6-benzyloxy-2-benzyloxycarbonyl)benzoyl)-3,5-dibenzyloxybenzoyloxy]-1-(2-benzyloxybenzamido)cyclopentane (COMPOUND 680)

To a solution of the amide alcohol from the preceding reaction (310 mg, 1.00 mmol) in CH_2Cl_2 (10 ml) were added

diisopropylethyl amine (174 L, 1.00 mmol, 1.0 eq), 4-dimethylaminopyridine (122 mg, 1.00 mmol, 1.0 eq), then a solution of the acid chloride (1.00 mmol) in CH_2Cl_2 (10 ml). The mixture was stirred at room temperature under N_2 for 17 h. The solution was then poured into 5% HCl (50 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated. The resulting oil was purified by flash column chromatography on silica gel (2:1 hexanes:ethyl acetate) to provide the title coupled product (0.58 g, 60%) as a tan foam: ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 7.8 Hz, 1H), 8.13 (d, J = 7.5 Hz, 1H), 7.4-7.5 (m, 5H), 7.15-7.3 (m, 15H), 7.05-7.15 (m, 9H), 6.93 (d, J = 7.9 Hz, 1H), 6.84 (d, J = 7.0 Hz, 2H), 5.14 (s, 2H), 5.13 (s, 2H), 4.9-5.0 (m, 1H), 4.78 (s, 4H), 4.69 (s, 2H), 4.55-4.65 (m, 1H), 2.1-2.2 (m, 1H), 1.8-1.95 (m, 1H), 1.65-1.8 (m, 2H), 1.4-1.5 (m, 1H), 1.25-1.4 (m, 1H).

(±)-Trans-2-[4-(6-hydroxy-2-(carboxyl)benzoyl)-3,5-dihydroxybenzyloxy]-1-(2-hydroxybenzamido)cyclopentane (COMPOUND 681)

To a round bottom flask containing Compound 680 (0.58 g, 0.60 mmol) and $Pd(OH)_2$ (290 mg, of a 20% by weight powder) were added THF (27 ml) and ethanol (27 ml). The flask was evacuated and filled with H_2 twice, then stirred under H_2 (1 atm) 7h, filtered through Celite, and evaporated. The mixture was divided into two portions and part (55%) was saved for methylation. The remaining 45% of the crude was purified by reverse phase HPLC (C18 column) to provide the title acid (85 mg, 59%) as a yellow powder after lyophilization: m.p. 128-124° (dec); ^1H NMR (300 MHz, CD_3OD) δ 7.56 (d, J = 8.1 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 7.13 (dd, J = 8.4, 8.3 Hz, 1H), 7.06 (dd, J = 7.9, 8.0 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.69 (s, 2H), 6.66 (m, 1H), 5.1-5.2 (m, 1H), 4.29 (dt, J = 7.5, 7.8 Hz, 1H), 2.0-2.1 (m, 2H), 1.65-1.75 (m, 2H), 1.45-1.65 (m, 2H); IR (KBr) 3369, 1703, 1636, 1602, 1246 cm^{-1}; MS m/e calc'd for $C_{27}H_{24}O_{10}N$ (M^+ + 1): 522.1400, found 522.1397; Analysis calc'd

for $C_{27}H_{23}NO_{10}$•0.6 TFA: C, 57.42; H, 4.03; N, 2.37; found: C, 57.61; H, 4.25; N, 2.45.

(±)-Trans-2-[4-(6-hydroxy-2-(methylcarboxyl)benzoyl]-3,5-dihydroxybenzoyloxy)-1-(2-hydroxybenzamido)cyclopentane (COMPOUND 682)

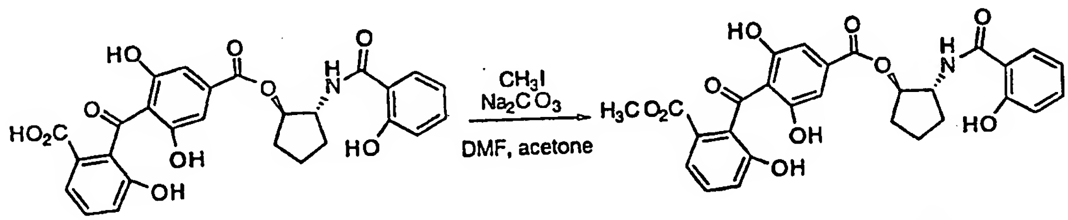


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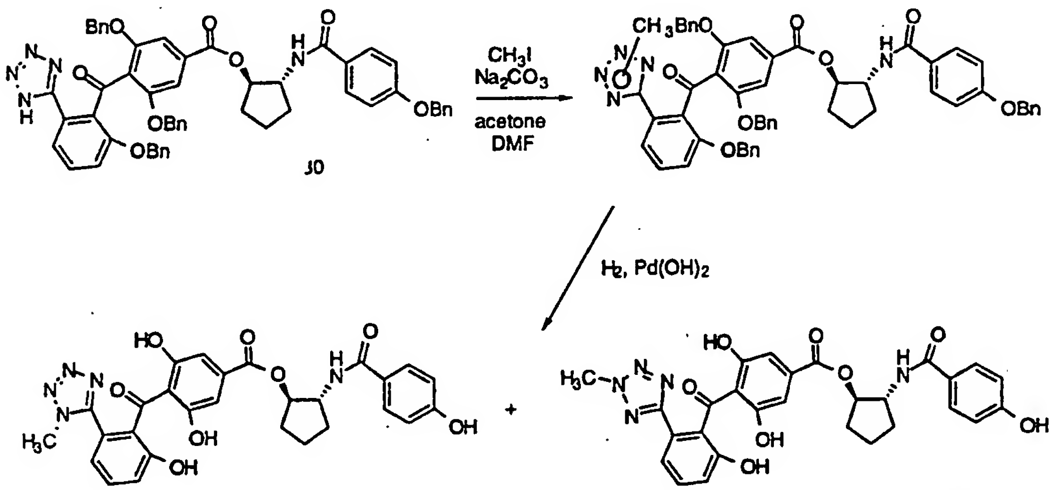
Figure AR

To a solution of Compound 681 (0.33 mmol) in acetone (9.7 ml) and DMF (9.7 ml) were added Na_2CO_3 (62 mg, 0.58 mmol, 1.5 eq) then iodomethane (121 L, 1.94 mmol, 5.0 eq). The mixture was stirred at room temperature 1 h, then more iodomethane (5.0 eq) was added. After stirring 1.5 h more, the mixture was poured into 5% HCl (50 ml) and ethyl acetate (40 ml). The layers were separated and the organic layer washed with H_2O (3 x 40 ml). The organic layer was dried ($MgSO_4$), filtered and evaporated. Purification by reverse phase HPLC (C18 column) provided the title ester (80.9 mg, 46%) as a yellow powder after lyophilization: m.p. 100-111° (dec); ^1H NMR (300 MHz, CD_3OD) δ 7.56 (d, J = 8.1 Hz, 1H), 7.25 (d, J = 7.7 Hz, 1H), 7.15 (dd, J = 7.6, 7.9 Hz, 1H), 7.07 (dd, J = 7.9, 8.1 Hz, 1H), 6.84 (d, J = 7.1 Hz, 1H), 6.71 (s, 2H), 6.6-6.7 (m, 2H), 5.11 (dt, J = 7.3, 4.9 Hz, 1H), 4.30 (dt, J = 10.1, 5.3 Hz, 1H), 3.48 (s, 3H), 2.0-2.1 (m, 2H), 1.6-1.75 (m, 2H), 1.45-1.6 (m, 2H); IR (KBr) 3379, 1705, 1637, 1602, 1303 cm^{-1}; MS m/e calc'd for $C_{28}H_{26}O_{10}N$ (M^+ + 1): 536.1557, found 536.1573; Analysis calc'd for $C_{28}H_{25}NO_{10}$° 0.6 TFA: C, 58.07; H, 4.27; N, 2.32; found: C, 57.95; H, 4.31; N, 2.48.

(±)-Trans-2-[4-(6-hydroxy-2-(2-methyltetrazolyl)benzoyl)-3,5-dibenzyloxybenzoyloxy]-1-(4-hydroxybenzamido)cyclopentan (COMPOUND 685) and (±)-Trans-2-[4-(6-hydroxy-2-(3-methyltetrazolyl)benzoyl)-3,5-dibenzyloxybenzoyloxy]-1-(4-hydroxybenzamido)cyclopentane (COMPOUND 686)



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(±)-Trans-2-[4-(6-benzyloxy-2-(2-methyltetrazolyl)benzoyl)-3,5-dibenzyloxybenzoyloxy]-1-(4-benzyloxybenzamido)cyclopentane

To a solution of (±)-Trans-2-[4-(6-benzyloxy-2-(2-tetrazoyl)benzoyl)-3,5-dibenzyloxybenzoyloxy]-1-(4-benzyloxy benzamido)cyclopentane (121 mg, 0.134 mmol) in acetone (3.3 ml) and DMF (3.3 ml) were added Na_2CO_3 (21 mg, 0.20 mmol, 1.5 eq) then iodomethane (83 μL, 1.34 mmol, 10 eq). The mixture was stirred at room temperature 1 h, diluted with ethyl acetate (40 ml) and washed with 5% HCl (30 ml) then H_2O (2 x 40 ml). The organic layer was dried ($MgSO_4$), filtered and evaporated. ^1H NMR of the crude reaction mixture showed signals consistent with a 1:1 mixture of two mono-methylated products, and the mixture was used for the deprotection step without attempt to separate the regioisomers.

(±)-Trans-2-[4-(6-hydroxy-2-(2-m thyltetrazolyl)benzoyl)-3,5-dibenzyloxybenzoyloxy]-1-(4-hydroxybenzamido)cyclopentane (COMPOUND 685) and (±)-Trans-2-[4-(6-hydroxy-2-(3-methyltetrazolyl)benzoyl)-3,5-dibenzyloxybenzoyloxy]-1-(4-hydroxybenzamido)cyclopentane (COMPOUND 686)

To a round bottom flask of the produce of the preceding reaction (0.134 mmol) were added $Pd(OH)_2$ (31 mg of a 20% by wt. powder) then THF (6.0 ml) and ethanol (6.0 ml). The flask was evacuated and filled with H_2 three times, then stirred under H_2 (1 atm) for 15.5 h. The slurry was filtered through Celite, washed through with methanol and evaporated. Purification by reverse phase HPLC (C18 column) provided Compound 685 (29.2 mg, 39%) and Compound 686 (26.4 mg, 35%), and a fraction containing a mix of the regioisomers (9.0 mg, 12%), each as a yellow powder after lyophilization: m.p. 150-158° (dec); ^{1}H NMR (300 MHz, CD_3OD) δ 7.47 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 7.7 Hz, 1H), 7.13 (dd, J = 8.1, 7.8 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 6.65 (s, 2H), 6.59 (d, J = 8.7 Hz, 2H), 5.06 (dt, J = 10.6, 5.3 Hz, 1H), 4.28 (dt, J = 13.6, 5.7 Hz, 1H), 3.98 (s, 3H), 1.95-2.1 (m, 2H), 1.4-1.7 (m, 4H); IR (KBr) 3394, 1704, 1609, 1244, 1201 cm^{-1}; MS m/e calc'd for $C_{28}H_{26}O_8N_5$ (M^+ + 1): 560.1781, found 560.1772; Analysis calc'd for $C_{28}H_{25}O_8N_5 \cdot 0.6$ TFA: C, 55.85; H, 4.11; N, 11.15; found: C, 55.61; H, 4.18; N, 11.08.

Anti-3-(4-hydr xybenzamid)-4-[4-(2-hydroxy-1-[5,6,7,8-t trahydro-naphthoyl])-3,5-dihydroxyb nzyoloxy]pyrrolidine trifluoroacetic acid salt (COMPOUND 687)

t-Butyl *anti*-3-(4-benzyloxybenzamido)-4-[4-(2-benzyloxy-1-naphthoyl)-3,5-dibenzyloxybenozyloxy]-N-pyrrolidinecarboxylate (COMPOUND 690)

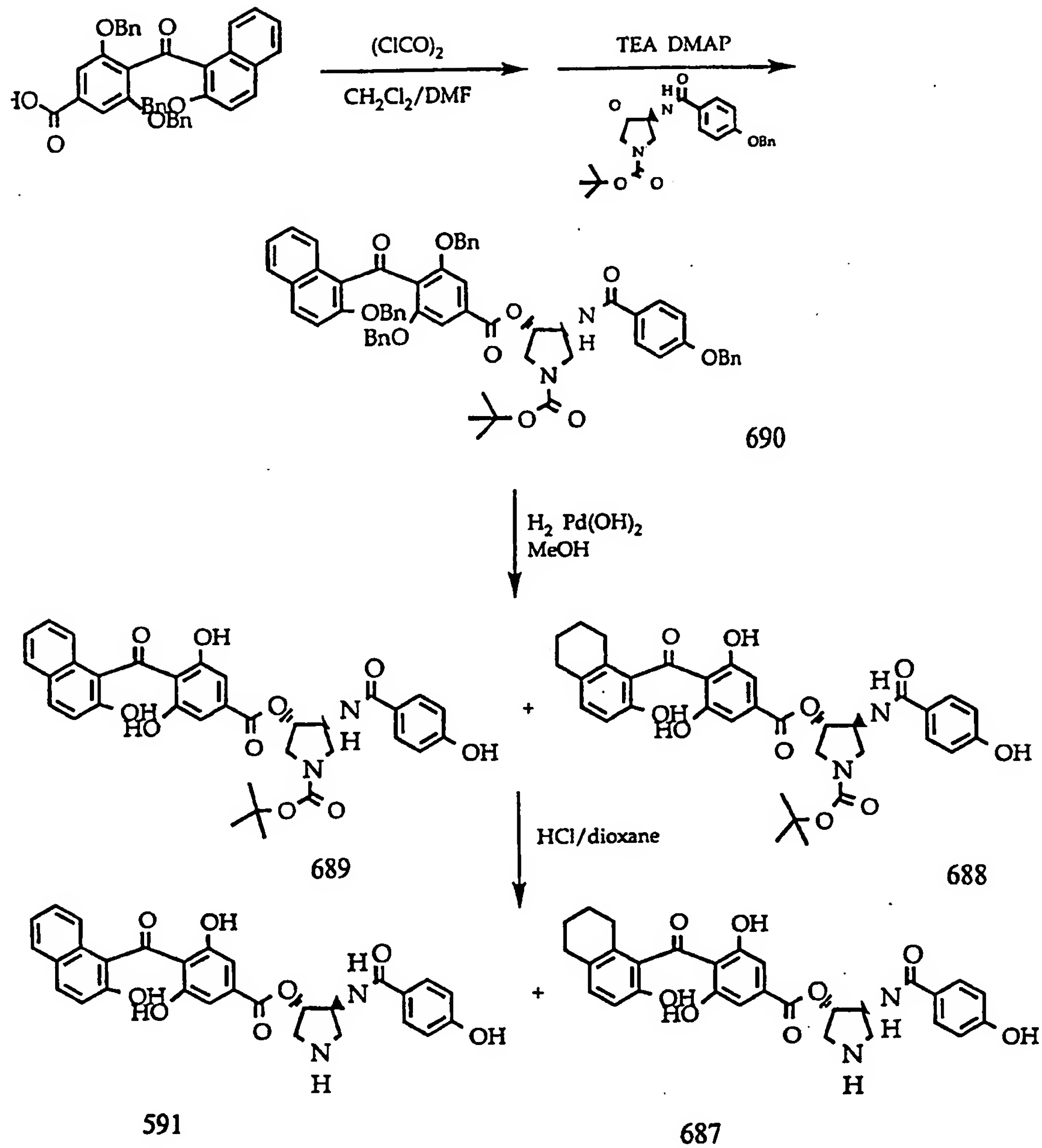
To a suspension of 4-(2-benzyloxy-1-naphthoyl)-3,5-dibenzyloxybenzoic acid (3.00 g, 5.04 mol) in dichloromethane (30 ml) with a catalytic amount of dimethylformamide at 0°C was added slowly oxalyl chloride (3.8 ml, 7.57 mol, 2.0 M in dichloromethane). After 1 1/2 hours, the solvent was evaporated off and the residue dried thoroughly under high vacuum for several hours. The acid chloride was then taken up in dichloromethane (20 ml) and canulated into a 0°C mixture of t-butyl *anti*-3-(4-benzyloxybenzamido)-4-hydroxy-N-pyrrolidinecarboxylate (2.08 g, 5.04 mol), triethyamine (2.1 ml, 15.1 mol), and dimethylaminopyridine (61 mg, 0.504 mol) in dichloromethane (30 ml). After 15 hours, the reaction mixture was diluted with dichloromethane (200 ml) and washed with water (100 ml). The organic layer was washed with brine (75 ml) and dried over magnesium sulfate, filtered, then concentrated down to an oil. The crude material was purified on a silica gel column (25-40% ethyl acetate/hexanes) to afford 3.38 g of Compound 690 as an off-white foam (68%).

t-Butyl *anti*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-1-[5,6,7,8-tetra-hydronaphthoyl])-3,5-dihydroxybenzyloxyl]-N-pyrrolidine-carboxylate (COMPOUND 689)

A mixture of Compound 690 (3.30 g, 3.34 mol) and Pearlman's catalyst (1.1g, 33% by weight) in methanol (90 ml) was shaken on a Parr apparatus under a hydrogen atmosphere at 52 psi for 18 hours. The catalyst was filtered off through a pad of Celite® and the filtrate was concentrated to give an oil (2.1g, 100%) as a mixture of Compound 689 and t-butyl *anti*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-1-naphthoyl)-3,5-dihydroxybenzoyloxy]-N-pyrrolidine-carboxylate (COMPOUND 689).

Anti-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-1-[5,6,7,8-tetrahydronaphthoyl])-3,5-dihydroxybenzoyloxy]pyrrolidine trifluoroacetic acid salt (COMPOUND 687)

2.1 g of Compound 689 (3.34 mol) was dissolved in a solution of HCl/dioxane (appr. 0.5 N, 75 ml). After 5 hours, the solvent was evaporated off and dried under high vacuum. The crude material was purified through extensive HPLC work to afford both Compound 687 (147 mg, 6%) and Compound 591 (287 mg, 11%). mp 180-181°C. ^{1}H NMR (ppm) δ 7.78 (d, 2 H, J = 8.5 Hz), 7.02 (s, 2 H), 6.92 (d, 1 H, J = 8.5 Hz), 6.86 (d, 2 H, J = 8.5 Hz), 6.59 (d, 1 H, J = 8.5 Hz), 5.63-5.65 (m, 1 H), 4.62-4.66 (m, 1 H), 3.96 (dd, 1 H, J = 7.5 Hz, J = 9 Hz), 3.83 (dd, 1 H, J = 7.5 Hz, J = 9 Hz), 3.55-3.65 (m, 2 H), 2.70 (t, 2 H, J = 5.5 Hz), 2.54 (t, 2 H, J = 6 Hz), 1.3-1.7 (m, 4 H). IR (KBr disc) cm^{-1} 3410, 3258, 2938, 2363, 1725, 1676, 1637, 1608, 1543, 1508, 1428, 1371, 1348, 1277, 1223, 1203, 1143, 1105, 1072, 1050, 991, 920, 848, 826, 801, 769, 723. Anal. calcd. for $C_{29}H_{28}N_2O_8 \cdot 1.5\ C_2HF_3O_2 \cdot 1\ H_2O$: C, 53.26; H, 4.40; N, 3.88. Found: C, 53.12; H, 4.38; N, 3.89. Mass spectral analysis: m/z (M + 1) = 533


(ClCO)$_2$
CH$_2$Cl$_2$/DMF
TEA DMAP
690
H$_2$ Pd(OH)$_2$
MeOH
689
688
HCl/dioxane
591
687

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Anti-4-[4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]hexahydro-3-(4-hydroxybenzoyl-N-methylamino)azepine, trifluoroacetic acid salt (COMPOUND 542)

Anti-hexahydro-4-(4-methylbenzoyloxy)-3-(4-phenylmethoxybenzoylamino)-1-phenylmethylazepine (COMPOUND 623)

An ice-cooled (5°C) solution of *anti*-hexahydro-4-hydroxy-3-(4-phenylmethoxybenzoylamino)-1-phenylmethylazepine (0.50 g, 1.16 mmol), 4-dimethylaminopyridine (50 mg), and triethylamine (0.5 mL) in anhydrous methylene chloride (8 mL) was treated dropwise with p-toluoyl chloride (0.24 g, 1.55 mmol) in methylene chloride (2 mL). The mixture was stirred at room temperature for 16h, then diluted with methylene chloride (25 mL) and stirred with saturated sodium bicarbonate (10 mL) for a few minutes. The organic layer was separated and the aqueous solution was extracted with methylene chloride (15mL). The combined organic solution was dried (Na_2SO_4) and concentrated in vacuo to a residue, which was chromatographed on silica gel (eluted with methylene chloride, then with 5% acetone/methylene chloride) to afford *anti*-hexahydro-4-(4-methylbenzoyloxy)-3-(4-phenylmethoxybenzoylamino)-1-phenylmethylazepine (0.60 g, 94%) (COMPOUND 623) as a viscous colorless oil.

Anti-hexahydro-4-(4-methylbenzoyloxy)-3-(4-phenylmethoxybenzoyl-N-methylamino)-1-phenylmethylazepine (COMPOUND 624)

A cooled solution of *anti*-hexahydro-4-(4-methylbenzoyloxy)-3-(4-phenylmethoxybenzoylamino)-1-phenylmethylazepine (0.59 g, 1.07 mmol) in anhydrous N,N-dimethylformamide (4 mL) under nitrogen was treated with lithiumbis(trimethylsilyl)amide/tetrahydrofuran (Aldrich, 1.15 mL, 1.15 mmol), stirred for 15 min at 5°C, then treated (via syringe) with dimethyl sulfate (109 μL, 0.145 g, 1.15 mmol). The mixture was stirred at room temperature for 1.5h, then added to a stirred mixture of methylene chloride (25 mL) and

saturated aqueous sodium bicarbonate (15 mL). The organic layer was separated and the aqueous solution was extracted with methylene chloride (15 mL). The combined organic solution was dried (Na_2SO_4), concentrated in vacuo, and the residue was chromatographed on silica gel (eluted with 1%, then 2%, then 3% acetone/methylene chloride) to afford *anti*-hexahydro-4-(4-methylbenzoyloxy)-3-(4-phenylmethoxybenzoyl-N-methylamino)-1-phenylmethylazepine (0.46 g, 76%) (COMPOUND 624) as a viscous colorless oil.

Anti-Hexahydro-4-hydroxy-3-(4-phenylmethoxybenzoyl-N-methylamino)-1-phenylmethylazepine

A solution of *anti*-hexahydro-4-(4-methylbenzoyloxy)-3-(4-phenylmethoxybenzoyl-N-methylamino)-1-phenylmethylazepine (0.46 g, 0.82 mmol) in reagent methanol (6 mL) was treated with 30% aqueous potassium hydroxide (2 g), and stirred at room temperature overnight. The solution was partially concentrated and diluted with water (10 mL). The aqueous solution was extracted with methylene chloride (3x20 mL), and the combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed on silica gel (eluted with ethyl acetate) to afford *anti*-hexahydro-4-hydroxy-3-(4-phenylmethoxybenzoyl-N-methylamino)-1-phenylmethylazepine (0.26 g, 72%) as a colorless viscous oil.

Anti-4-[3,5-Bis(phenylmethoxy)-4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)benzoyloxy]hexahydro-3-(4-phenylmethoxy)-benzoyl-N-methylamino-1-phenylmethylazepine (COMPOUND 625)

A solution of 3,5-bis(phenylmethoxy)-4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)benzoic acid (0.25 g, 0.37 mmol) in anhydrous methylene chloride (1.5 mL) was treated with N,N-dimethylformamide (3 drops), then with 2.0N oxalyl chloride/methylene chloride (Aldrich, 0.25 mL, 0.50 mmol), and stirred for one hour under nitrogen. The solution was concentrated in vacuo, placed under high vacuum for one hour, and set aside under nitrogen. *Anti*-Hexahydro-4-hydroxy-3-(4-phenylmethoxybenzoyl-N-methylamino)-1-phenylmethylazepine (0.18

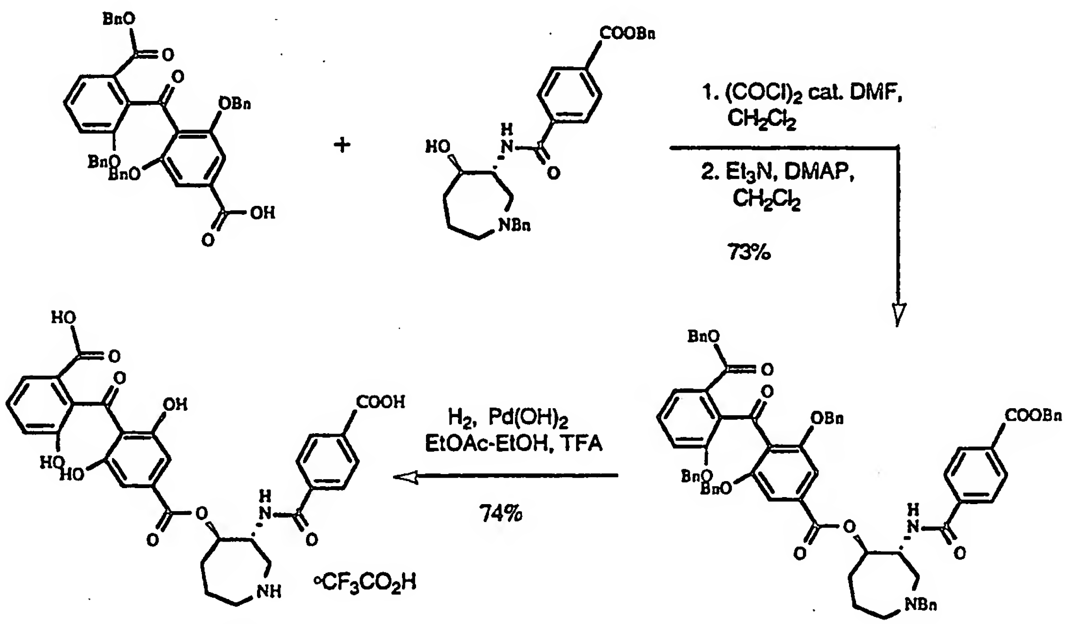
g, 0.40 mmol) was dissolved in methylene chloride (1.5 mL) under nitrogen, then treated with 4-dimethylaminopyridine (30 mg), triethylamine (0.20 mL), and a solution of the above formed acid chloride in methylene chloride (1.5 mL). The mixture was stirred for 18h, concentrated in vacuo, and chromatographed on silica gel (eluted successively with 2.5% acetone/methylene chloride, 5% acetone/ methylene chloride, and 5% methanol/methylene chloride) to afford, initially, *anti*-4-[3,5-bis(phenylmethoxy)-4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)benzoyloxy]hexahydro-3-(4-phenylmethoxy) benzoyl-N-methylamino-1-phenylmethylazepine (110 mg) (COMPOUND 625), then recovered *anti*-hexahydro-4-hydroxy-3-(4-phenylmethoxybenzoyl-N-methylamino)-1-phenylmethylazepine(120 mg). The yield based on recovered starting material was 74%.

***Anti*-4-[4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]hexahydro-3-(4-hydroxybenzoyl-N-methylamino)azepine, trifluoroacetic acid salt (COMPOUND 542)**

A solution of *anti*-4-[3,5-bis(phenylmethoxy)-4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)benzoyloxy]hexahydro-3-(4-phenylmethoxy)benzoyl-N-methylamino)-1-phenylmethylazepine (0.11 g, 0.10 mmol) in 2:1 ethanol/ethyl acetate (15 mL) under nitrogen in a Parr bottle was treated with trifluoroacetic acid (50 μL), then with 20% $Pd(OH)_2/C$ (80 mg), and was placed under 50 psi hydrogen pressure in a Parr apparatus for 16h. The bottle was carefully evacuated of hydrogen, the solution was filtered through celite, and the filter cake was washed with ethanol without allowing it to dry. The filtrate was concentrated in vacuo and the residue was dissolved in DMF (0.4 mL) and loaded onto an HPLC column; conditions: A-0.1%TFA/5% $MeCN/H_2O$, B-MeCN, 100% A to 50:50 A:B over 60 min, 15 mL/min, 21x250 cm C_{18} column. Fractions (one/min) 27-29 were combined, partially concentrated, and freeze-dried overnight to afford *anti*-4-[4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]hexahydro-3-(4-hydroxybenzoyl-N-methylamino)azepine, trifluoroacetic acid salt (35 mg, 48%) (COMPOUND 542) (as a pale yellow voluminous solid; mp 168-

172°C. R_f (6:1:1 n-BuOH/AcOH/H_2O on silica) 0.45; IR (KBr): 1677, 1634, 1608 cm^{-1}; ^1H NMR (d_6-DMSO) δ 11.73 (s, 2H), 9.92 (s, 2H), 9.15 (br s, 1H), 8.90 (br s, 1H), 7.39 (d, 1H, J = 8Hz), 7.30 (t, 1H, J = 8Hz), 7.15 (d, 2H, J = 8 Hz), 7.08 (d, 1H, J = 8 Hz), 6.83 (s, 2H), 6.76 (d, 2H, J = 8 Hz), 5.55 (m, 1H), 4.60 (m, 1H), 3.30 - 3.70 (m, 2H), 3.05 - 3.25 (m, 2H), 2.88 (s, 3H), 2.05 - 2.20 (m, 1H), 1.80 - 2.05 (m, 3H); mass spectrum (FAB): m/z 565. Anal. Calcd. for $C_{29}H_{28}N_2O_{10}$ ° 1.2($C_2HO_2F_3$) ° 1.5(H_2O): C, 51.78; H, 4.46; N, 3.84. Found: C, 51.84; N, 4.32; N, 3.95.

(±)-Trans-3-(4-Benzyloxycarbonylbenzamido)-4-[4-(2-carboxy-6-hydroxy)benzoyl-3,5-dihydroxy]benzoyloxyhexahydroazepine trifluoroacetic acid salt (COMPOUND 674)



674 673

Figure AU

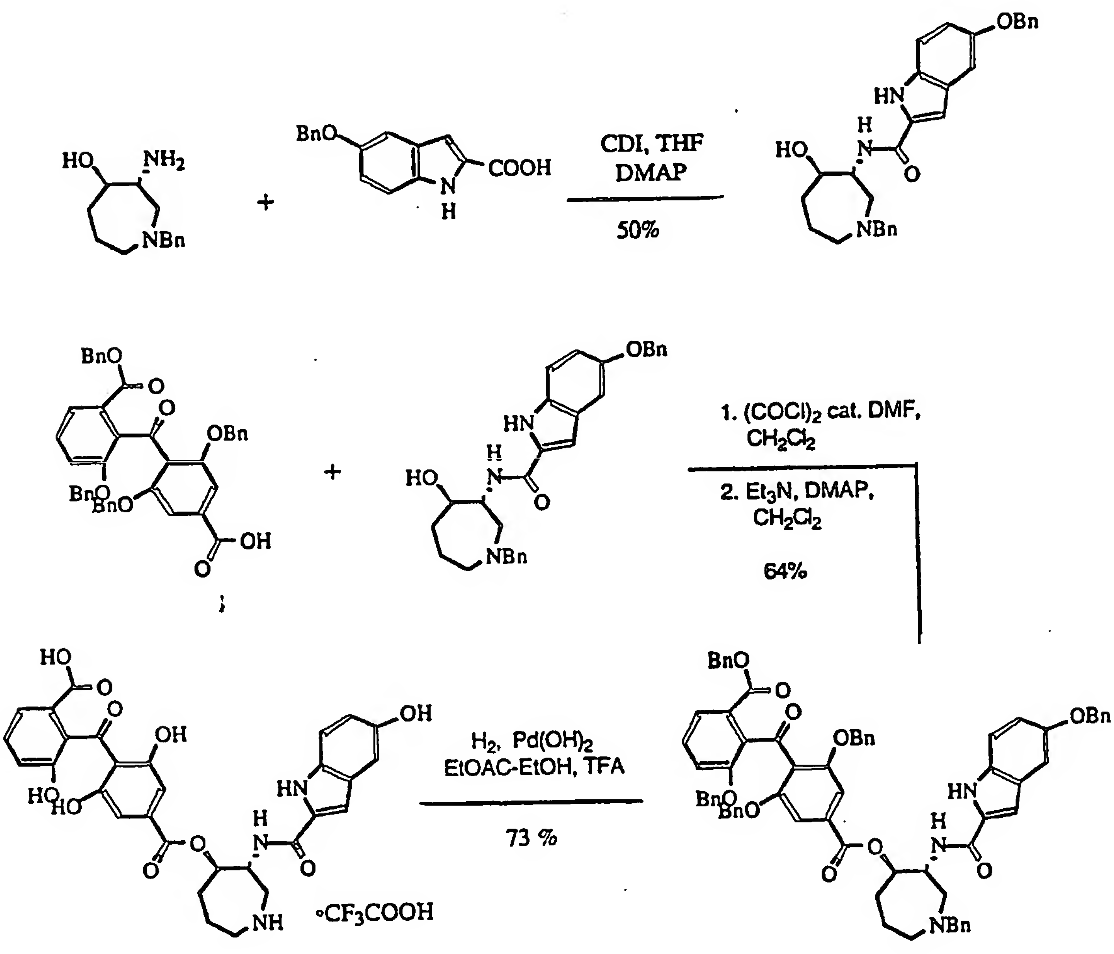
To a solution of benzophenone acid (SPC 104034, 252mg, 0.371mmol) in CH_2Cl_2 (3mL) was added cat. DMF and oxalyl

chloride (2.0 M solution in CH_2Cl_2, 0.464mL, 0.93mmol) at room temperature. The mixture was stirred at room temperature for 2 hr. Solvents were removed and the acid chloride residue was taken into CH_2Cl_2 (5mL) after drying over the vacuum for 1 hr.

A solution of amidoalcohol (SPC 104101, 170.2mg, 0.371mmol), Et_3N (187.8mg, 259μL, 1.86mmol) and DMAP (45.4mg, 0.371mmol) in CH_2Cl_2 (5 mL) was treated with the freshly made acid chloride-CH_2Cl_2 solution (5 mL) at 5°C. The reaction mixture was allowed to stir at room temperature for overnight and then chromatographed on silica gel with 2:3/EtOAc:Hexane as an eluent to afford light yellow solids (300mg, 73%) (COMPOUND 673).

Compound 673 (285mg, 0.25mmol) was dissolved in EtOAc-EtOH (1:1, 20 mL) and treated with TFA (cat.) followed by 10% Pd/C (165mg, 60mol%). The mixture was subjected to hydrogenolysis at 50 psi for 20hr. Solvents were concentrated after filtering through a pad of celite, and the residue was dissolved in DMF (0.75 mL) and loaded onto HPLC; conditions: A-0.1%TFA/5%CH_3CN/H_2O, B-100%CH_3CN, 0-50%B over 60 min, 25 mL/min, 41x300 mm C18 column. Fractions (one/min) 38-41 were combined, concentrated, and lyophilized to afford fluffy yellow solids (128mg, 74%)(COMPOUND 674). m.p. 204-206 (dec)°C; ^1H nmr (CD_3OD) δ 8.06 (d, J = 8.5 Hz, 2H, ArH), 7.80 (d, J = 8.3 Hz, 2H, ArH), 7.48 (d, J = 7.7 Hz, 1H, ArH), 7.26 (t, 1H, ArH), 7.01 (d, J = 9.3 Hz, 1H, ArH), 6.89 (s, 2H, ArH), 5.45 (m, 1H, CH-4), 4.49 (m, 1H, CH-3), 3.51 (d, J = 5.8 Hz, 2H, NCH_2), 2.31-2.00 (m, 4H, $2CH_2$); IR (KBr) cm^{-1} 3387, 3340, 3233, 3080, 1704, 1676, 1636, and 1606. Anal. Calcd. for $C_{29}H_{26}N_2O_{11}$ • $1.25H_2O$ • $1.5C_2HF_3O_2$: C, 49.78; H, 3.92; N, 3.63. Found: C, 49.88; H, 3.70; N, 3.68. LRFAB (M + 1): 579.

(+)-*Trans*-4-[4-(2-carboxy-6-hydroxy)b nzoyl-3,5-dihydroxy]benzoyloxy-3-[2-(5-hydroxyindolyl)f rmamido]-hexahydroazepine trifluoroacetic acid salt (COMPOUND 672)



672 671

Figure AV

To a solution of 5-benzyloxy-2-indolylcarboxylic acid (Lancaster, 509.6 mg, 1.91mmol) in anhydrous THF (5mL) was added CDI (324mg, 2.0mmol). The resulting mixture was stirred at room temperature for 2h prior to treatment with DMAP (44.36mg, 0.36mmol) and a solution of N-benzyl-3-amino-4-

hydroxyhexahydroazepine (SPC 104004, 400mg, 1.82mmol) in THF (3mL). Solvents were removed *in vacuo* after reaction at room temperature for overnight. The residue was taken into CH_2Cl_2-petroleum ether to precipitate white crystals, which were collected and rinsed with CH_2Cl_2 to afford the product (416mg, 50%).

To a solution of benzophenone acid (255mg, 0.38mmol) in CH_2Cl_2 (3mL) was added cat. DMF and oxalyl chloride (2.0 M solution in CH_2Cl_2, 0.47mL, 0.94mmol) at room temperature. The mixture was stirred at room temperature for 2hr. Solvents were removed and the acid chloride residue was taken into CH_2Cl_2 (5mL) after drying over the vacuum for 1hr.

A solution of amidoalcohol (176.4 mg, 0.37mmol), Et_3N (190mg, 262μL, 1.88mmol) and DMAP (46mg, 0.376mmol) in CH_2Cl_2 (5mL) was treated with the freshly made acid chloride-CH_2Cl_2 solution (5mL) at 5°C. The reaction mixture was allowed to stir at room temperature for 3h and then chromatographed on silica gel eluting with 2:3/EtOAc:Hexane to afford the product as light yellow solids (270 mg, 64%) (COMPOUND 671).

The product of the preceding reaction (240mg, 0.212mmol) was dissolved in EtOAc-HOEt (1:1, 20mL) and treated with TFA (cat.) followed by 10% $Pd(OH)_2$ (140mg, 62mol%). The mixture was subjected to hydrogenolysis at 50 psi for 18hr. Solvents were concentrated after filtering through a pad of celite, and the residue was dissolved in DMF (1.0mL) and loaded onto an HPLC; conditions: A-0.1%TFA/5%CH_3CN/H_2O, B-100%CH_3CN, 0-50%B over 60 min, 25mL/min, 41X300 mm C18 column. Fractions (one/min) 38-42 were combined, partially concentrated, and lyophilized to afford fluffy yellow solids (109mg, 73%) (COMPOUND 672). m.p. 210-213 (dec)^{0}C; 1H nmr (CD_3OD) δ 7.27 (d, J = 7.5 Hz, 2H, ArH), 7.07-7.00 (t and d, 2H, ArH), 6.79 (d, J = 8.3 Hz, 1H, ArH), 6.70 (d, J = 2.3 Hz, 1H, ArH), 6.68 (s, 2H, ArH), 6.66 (s, 1H, ArH), 6.59 (dd, J = 2.5, 8.8 Hz, 1H, ArH), 5.25 (m, 1H, CH-4), 4.25 (m, 1H, CH-3), 3.30 (d, J = 5.4Hz, 2H, NCH_2), 2.10-1.78 (m, 4H), CH_2). IR (KBr) cm^{-1} 3398, 3307, 1699, 1682, 1676, and 1635. Anal. Calcd. for $C_{30}H_{27}N_3O_{10}$ • $.75H_2O$ •

$1.5C_2HF_3O_2$: C, 51.20; H, 3.91; N, 5.43. Found: C, 51.20; H, 4.05; N, 5.52. LRFAB (M + 1): 590.

Syn-4-[4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyl-N-methylamino]hexahydro-3-(4-hydroxybenzoylamino)azepine, trifluoroacetic acid salt (COMPOUND 543)

Hexahydro-4-(methylamino)-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine, mixture of isomers

A solution of hexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepin-4-one (0.37 g, 0.86 mmol) in reagent ethanol (5mL) was treated with N-methylhydroxylamine hydrochloride (0.11 g, 1.3 mmol) and with 25% methanolic sodium methoxide (0.28 g, 1.3 mmol). The mixture was stirred at room temperature for 3h, diluted with methylene chloride (20 mL), and filtered through celite. The filter pad was washed with methylene chloride and the filtrate was concentrated *in vacuo*, dissolved in reagent ethanol (25 mL) and placed in a Parr bottle. Raney nickel (one-half tsp) was carefully added under nitrogen, and the mixture was subjected to hydrogenation for 4h (needed longer) at 48-50 psi. The bottle was carefully evacuated of hydrogen and the solution was filtered through celite. The filter pad was washed with ethanol, with care taken not to let it become dry. The filtrate was concentrated *in vacuo* and the residue chromatographed on silica gel (eluted with 85:15 methylene chloride/isopropanol, then with 0.5% Et_3N/85:15 methylene chloride/IPA) to afford hexahydro-4-(methylamino)-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.18 g, 47%) as a mixture of isomers (syn:anti = 1:2 by NMR).

Syn-4-[3,5-Bis(phenylmethoxy)-4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)benzoyl-N-methylamino]hexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (COMPOUND 626)

A solution of 3,5-bis(phenylmethoxy)-4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)benzoic acid (0.25 g,

0.37 mmol) in anhydrous methylene chloride (1.5 mL) was treated with N, N-dimethylformamide (3 drops), then with 2.0 N oxalyl chloride/methylene chloride (Aldrich, 0.25 mL, 0.50 mmol) and stirred for one hour under nitrogen. The solution was concentrated *in vacuo*, placed under high vacuum for one hour, then dissolved in methylene chloride (2mL) and combined with hexahydro-4-(methylamino)-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.18 g, 0.40 mmol). The mixture was treated with 1.0N sodium hydroxide (1.0 mL) and stirred for two hours, then diluted with methylene chloride (10mL) and water (4mL). The organic layer was separated and the aqueous solution was extracted with methylene chloride (10mL). The combined organic solution was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed on silica gel (eluted successively with 4%, 5%, and 7% acetone/methylene chloride) to afford *syn*-4-[3,5-bis(phenylmethoxy)-4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)benzoyl-N-methylamino]hexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (80 mg) (COMPOUND 626), followed by the anti isomer (150 mg); combined yield 0.23 g (56%).

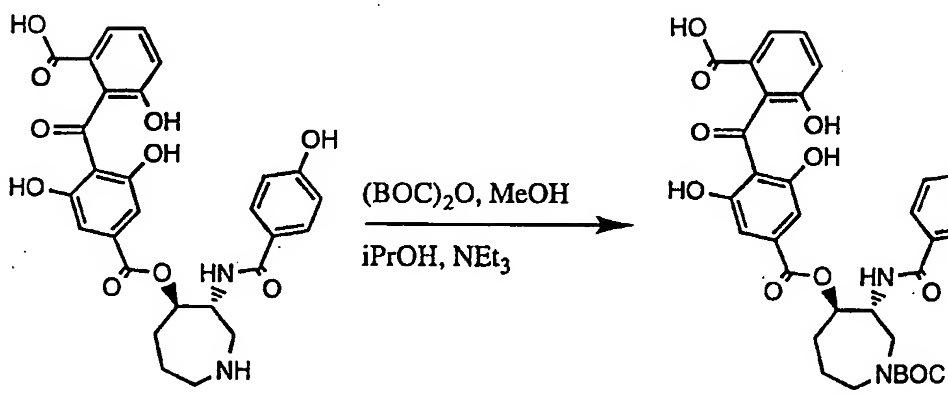
Syn-4-[4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyl-N-methylamino]hexahydro-3-(4-hydroxybenzoylamino)azepine, trifluoroacetic acid salt (COMPOUND 543)

A solution of *syn*-4-[3,5-bis(phenylmethoxy)-4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)benzoyl-N-methylamino]hexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (80 mg, 0.072 mmol) in 2:1 ethanol/ethyl acetate (12mL) under nitrogen in a Parr bottle was treated with trifluoroacetic acid (50 μL), then with 20% $Pd(OH)_2/C$ (70 mg), and was placed under 50 psi hydrogen pressure in a Parr apparatus for 20h. The bottle was carefully evacuated of hydrogen, the solution was filtered through celite, and the filter cake was washed with ethanol without allowing it to dry. The filtrate was concentrated *in vacuo* and the residue was dissolved in DMF (0.4 mL) and loaded onto an HPLC column; conditions: A-0.1%TFA/5% MeCN/H20, B-MeCN, 100% A to 50:50 A:B

over 60 min, 15 mL/min, 21X250 cm C_{18} column. Fractions (one/min) 25-27 were combined, partially concentrated, and freeze-dried overnight to afford *syn*-4-[4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyl-N-methylamino]hexahydro-3-(4-hydroxybenzoylamino)azepine, trifluoroacetic acid salt (37 mg, 70%) (COMPOUND 543) as a voluminous white solid; mp 290-5°C(dec). R_f (6:1:1 n-BuOH/AcOH/H2O on silica) 0.45; IR (KBr): 1676, 1634, 1607 cm^{-1}; ^1H NMR[1] (d_6-DMSO) δ 12.80 (br s, 1H), 11.68 (m, 2H), 10.08 (s, 1H), 9.83 (s, 1H), 8.90 (br s, 1H), 8.70 (br s, 1H), 8.13 (d, 1H, J = 9Hz), 7.75 (d, 2H, J = 8 Hz), 7.37 (d, 1H, J = 8 Hz), 7.26 (t, 1H, J = 8Hz), 705 (d, 1H, J = 8 Hz), 6.83 (d, 2H, J = 8 Hz), 6.14 (s, 2H), 4.90-5.05 (m, 1H), 4.50-4.60 (m, 1H), 3.05-3.50 (m, 4H), 2.73 (s, 3H), 2.20-2.40 (m, 1H), 1.70-2.10 (m, 3H); mass spectrum (FAB): m/z 564. Anal. Calcd. for $C_{29}H_{29}N_3O_9$ ∘ 1.1($C_2HO_2F_3$) ∘ 2(H_2O): C,51.69; H, 4.74; N, 5.80. Found: C, 51.46; H, 4.68; N, 5.80.

[1]Rotomeric effect observed in NMR spectrum.

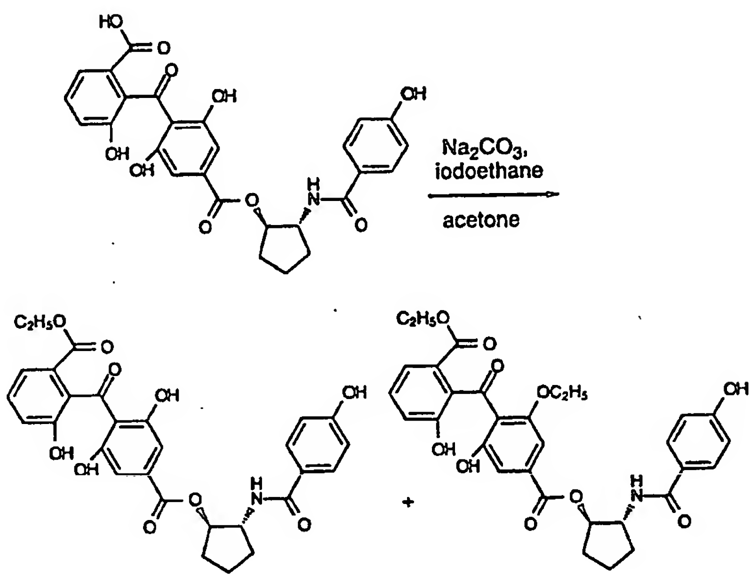
BOC-Balanol (COMPOUND 711)



711

Synthetic (-)-balanol (20 mg, 29.3 μmol) was dissolved in isopropanol and methanol (4:1,1 mL tot.), treated with di-*t*-butyl dicarbonate (10 μL, 9.6 mg, 44 μmol) and triethylamine (10 μL) and stirred for 16 h. The mixture was concentrated and the residue was chromatographed on a Dynarnax®-60 C_{18} column (21 X 250 mm) using a linear gradient from 100% A (0.1% TFA and 5% acetonitrile in water) to 50% B (pure acetonitrile) over 60 min at 15 mL/min. The clean product, which eluted in 53 min, was concentrated and scraped out to give synthetic BOC-balanol as a light yellow powder (13 mg, 68%) (COMPOUND 711). m.p. (dec.)200 °C; ^{1}H-NMR (300 MHz, dmso-d_6) δ occurs as a = 3:2 rotameric mixture 2.49 &2.50 (1:3 9H, s's), 1.6-2.0 (4H, m's), 3.1-3.7 (4H, m's), 4.24 (1H, m), 5.03 (1h, m), 6.72-6.78 (4H, d & s), 7.03 (1H, d), 7.26 (1H, t), 7.34, (1H, d), 7.58-7.66 (2H, d's), 8.12 (1H, NH); IR (KB3r): 3393, 1701, 1636, 1507, 1425, 1242 cm^{-1}; Anal. Calcd. for $C_{33}H_{34}N_2O_{12}$ • 2.5H_2O C, 56.97; H, 5.65; N, 4.03. Found: C, 56.81; H, 528; N, 4.21.

Anti-1-[4-(2-Ethoxycarbonyl-6-hydroxybenzoyloxy]-2-(4-hydroxybenzamido)cyclopentane

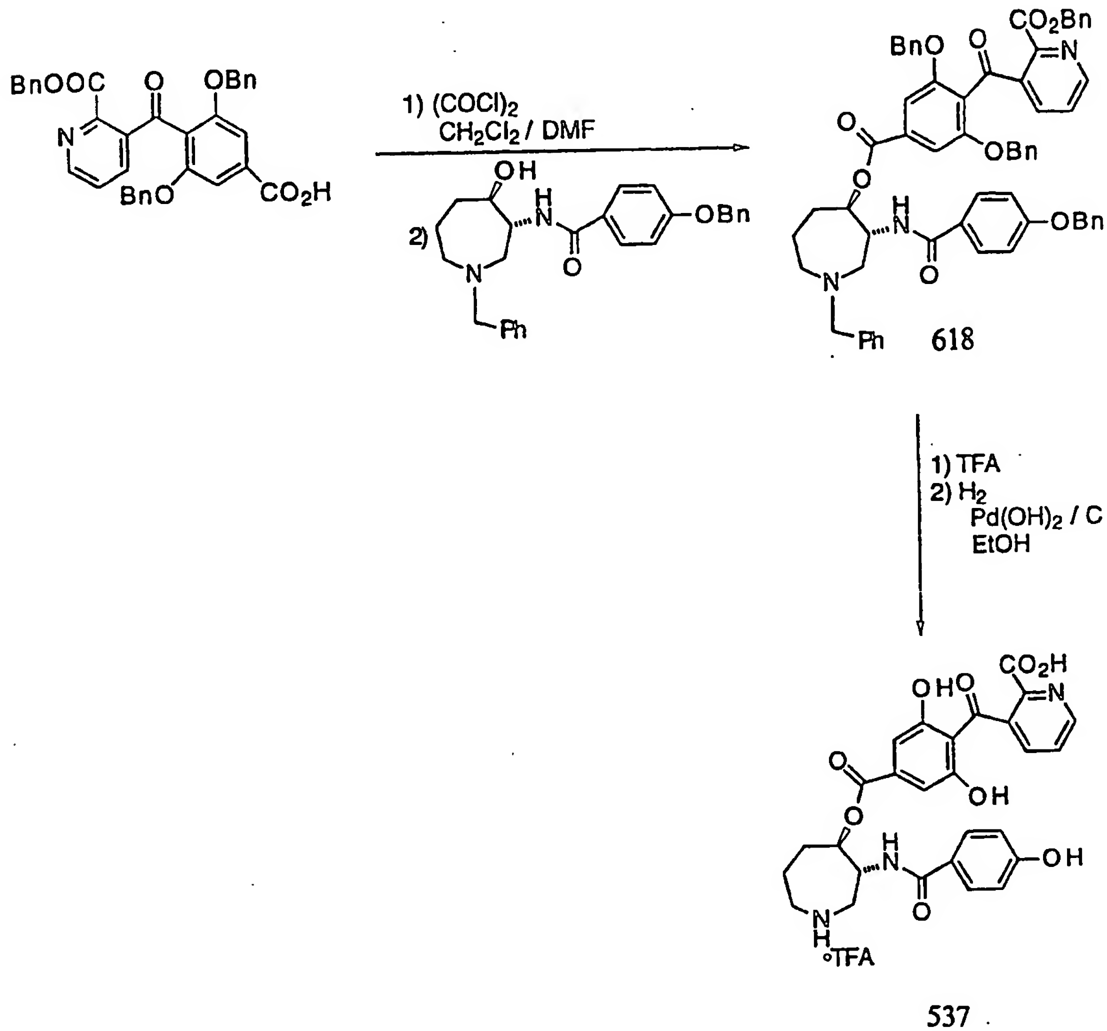


714 715

To a stirred solution of Compound 708 (DSM474-80A, 0.15 mmol, 80 mg) in acetone (10 mL) was added anhydrous granular sodium carbonate (0.31 mmol, 33 mg) in one portion, and the reaction flask was purged with nitrogen at room temperature. Iodoethane (large excess, 10 mmol, 1.5 g) was added *via* syringe, and the deep yellow reaction mixture was stirred at room temperature for 24 hours. The solvent was evaporated *in vacuo* and the crude yellow solid was partitioned between ethyl acetate (100 mL) and water (25 mL). The organic layer was then washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Compound 714 was purified *via* HPLC (21 x 250 mm C18 reverse phase column, pump A: 5% acetonitrile in water + 0.1 trifluoroacetic acid; pump 13: 100% acetonitrile; 0-100% pump 13 over 120 minutes,

flow rate = 15 mL/min, retention time = 54.8 minutes). The purified fractions were concentrated and the water removed by lyophilization to give 19.2 mg (23% purified yield) of the title compound as a bright yellow solid. IR (KBr): 1707, 1626, 1601, 1425, 1402, 1347, 1294, 1246, 1194 cm^{-1}. EA (calculated for $C_{29}H_{27}NO_{12}$ • 2.3 H_2O): C, 58.94; H, 5.39; N, 2.37. Found: C, 58.65; H, 5.02; N, 2.32. MS (m/e, low resolution FAB): $[M + H]^+$ = 550; $[M + Na]^+$ = 573.

4-R*-4-[((2-(Hydroxycarbonyl)-3-pyridinyl)carbonyl)-3,5-dihydroxybenzoyloxy]-3-R*-(4-hydroxybenzamido)azepine triflu roac tic acid (COMPOUND AY)



Trans-N-Benzyl-4-[(((2-benzyloxycarbonyl)-3-pyridinyl) carbonyl)-3,5-dibenzyloxybenzoyloxy]-3-(4-benzyloxybenzamido)azepine (COMPOUND 618)

Carbonyldiimidizole (0.110 g, 0.672 mmole) was added to a solution of 4-[((2-(benzyloxycarbonyl)-3-pyridinyl) carbonyl]-3,5-dibenzyloxybenzoic acid (0.275 g, 0.448 mmole) in 3 mL of methylene chloride containing a trace (approximately 1 μL) of dimethylformamide The solution was stirred at room temperature for sixty minutes under nitrogen. The solution was

added to a solution of 0.193 g (0.448 mmole) of trans-N-benzyl-3-(4-benzyloxybenzamido)-4-hydroxyazepine, 0.1 mL (0.672 mmole) of triethylamine, 5 mg of DMAP in 3 mL of methylene chloride. The solution was stirred at room temperature under nitrogen for sixteen hours. The solution was diluted with 30 mL of methylene chloride, washed with water, saturated brine and dried over magnesium sulfate. The solvent was removed in vacuo. The residue was chromatographed on silica gel eluting with a gradient of 5% - 10% - 20% ethyl acetate - hexane to yield 0.25 g (57%) of a clear oil (COMPOUND 618).

4-R*-4-[((2-(Hydroxycarbonyl)-3-pyridinyl)carbonyl)-3,5-dihydroxybenzoyloxy]-3-R*-(4-hydroxybenzamido)azepine trifluoroacetic acid (COMPOUND 537)

A solution of 0.250 g (0.254 mmole) of trans-N-benzyl-4-4-[(((2-benzoyloxycarbonyl)-3-pyridinyl)carbonyl)-3,5-dibenzyloxybenzoyloxy]-3-(4- benzyloxybenzamido)azepine in 10 mL of ethanol - methylene chloride (1 : 1) was treated with 0.040 mL (0.510 mmole) of trifluoroacetic acid. The solution was stirred at room temperature for fifteen minutes. The solvent was evaporated and the ethanol - methylene chloride solvent was added twice more and evaporated in order to remove the excess trifluoroacetic acid. The residue was taken up in 15 mL of ethanol and cooled to 0°C under nitrogen, and 0.030 g (0.025 mmole) of palladium hydroxide on carbon was added. The reaction mixture was stirred under an atmosphere of hydrogen for six hours. The reaction mixture was filtered, evaporated and the residue was chromatographed on a 41 x 250 mm C18 column (solvent A: 95 : 5 water / acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0 - 50% B over 60 min., flow 25 mL/min.). The pure fractions were pooled and evaporated to yield 0.011 g (5.6%) of a tan powder, mp 230-235°C (dec.) (COMPOUND 537). IR (KBr): 3420, 1683, 1610, 1542, 1434, 1341, 1240, 1202, 769. Anal. Calcd for $C_{27}H_{25}N_3O_9 \cdot 3H_2O \cdot 1.6$ TFA: C, 46.99; H, 4.26; N, 5.44. Found: C, 46.66; H, 4.64; N, 5.36.

(±)-*Anti*-3-(4-Methylphenylsulfonamido)-4-[3,5-dihydroxy-4-(2-hydroxy-6-carboxy)ph nylcarbonyl]benzoyloxyhexahydroazepine trifluoroac tic acid salt (COMPOUND 526)

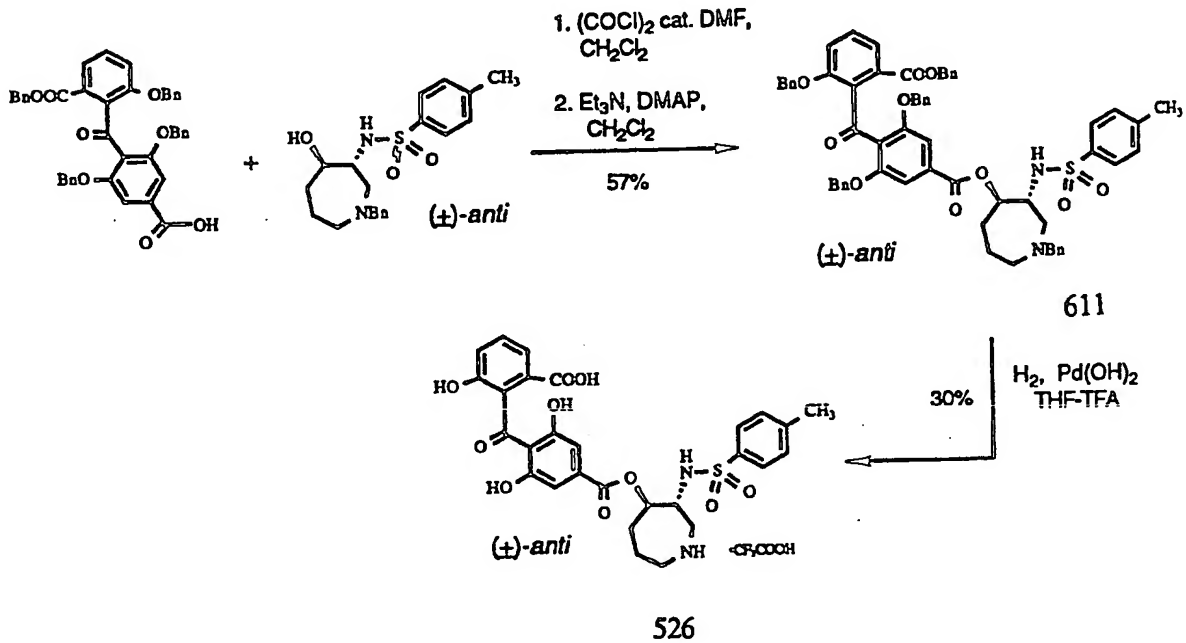


FIGURE AZ

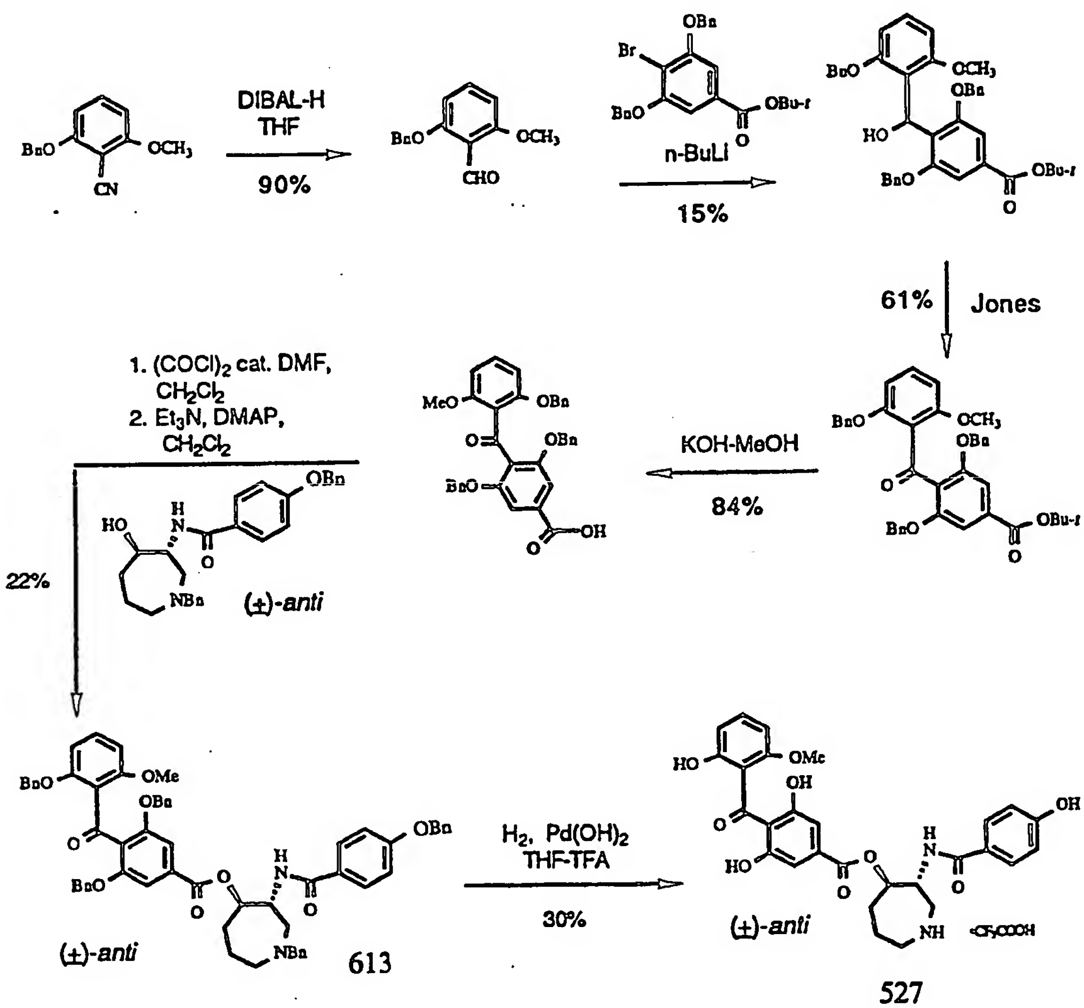
To a solution of benzophenone acid (304.7 mg, 0.449 mmol) in CH_2Cl_2 (3mL) was added cat. DMF and oxalyl chloride (2.0 M solution in CH_2Cl_2, 561 μL, 1.123 mmol) at room temperature. The mixture was stirred at room temperature for 1 hr. Solvents were removed and the acid chloride residue was taken into CH_2Cl_2 (5mL) after drying over vacuum for 1 hr.

The solution of azepine alcohol (168.1 mg, 0.449 mmol), Et_3N (227.19 mg, 312.9 μL, 2.245 mmol) and DMAP (10.97 mg, 0.089 mmol) in CH_2Cl_2 (5mL) was treated with the freshly made acid chloride-CH_2Cl_2 solution at 5°C. The reaction mixture was allowed to stir at room temperature for 3 hr and then chromatographed on silica gel eluting with 3:2 / hexane:EtOAc. The product was obtained as white solid (267 mg, 57%) (COMPOUND

611).

The product from the preceding reaction (250 mg, 0.24 mmol) was dissolved in THF (20 mL) and treated with a few drops of TFA and 20% $Pd(OH)_2/C$ (125 mg, 50% by weight). The mixture was placed in a Parr shaker and subjected to hydrogenolysis at 50 psi for overnight. THF was removed *in vacuo* and the residue taken into MeOH. The MeOH solution was concentrated after filtering through a pad of celite and chromatographed on a 41 x 300 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0-100% B over 60 min, flow: 25 mL/min). Two pure fractions were evaporated to give yellow solids. The one with longer retention time (Rt) remained to be identified (60 mg). The another with shorter Rt was identified as Compound 526 (50 mg, 30%). m.p. 162-165 (dec)°C; 1H nmr (CD_3OD) δ 7.62 (d, J = 8.3Hz, 2H, ArH), 7.52 (d, J = 7.7Hz, 1H, ArH), 7.28 (t,J = 7.7 and 8.2Hz, 1H, ArH), 7.13 (d, J = 8.1Hz, 2H, ArH), 7.04 (d, J = 8.2Hz, 1H, ArH), 6.58 (s, 2H, ArH), 5.05 (m, 1H, H-4), 3.72 (m, 1H, H-3), 3.51 (m, 2H, H-7 or H-2), 3.25 (m, 2H, H-2 or H-7), 2.10-1.90 (m, 4H, H-5 and H-6); lR (KBr) cm^{-1} 3432, 3182, 1677, 1635, 1602, and 1427. Anal. Calc. for $C_{28}H_{28}N_2O_{10}S \cdot 2.5H_2O \cdot TFA$: C, 48.45; H, 4.61; N, 3.77, S, 4.31. Found: C, 48.66; H, 4.27; N, 3.49, S, 3.98. LRFAB (M + 1): 585.

(±)-*Anti*-3-(4-hydroxybenzamido)-4-[3,5-dihydroxy-4-(2-hydroxy-6-methoxy)phenylcarbonyl]benzoyloxyhexahydroazepine trifluoroac tic acid salt (COMPOUND 527)



2-Benzyloxy-6-methoxybenzonitrile (2.0 g, 8.36 mmol) was dissolved in THF (20 mL) and cooled to -10°C. The DIBAL-H (1.0 M in Hexane, 8.5 mL, 8.5 mmol) was then added and the reaction was allowed to warm up to room temperature and stirred for 2 hr. H_2O (10 mL) was slowly added to the reaction,

resulting in heat generation. Solids precipitated were filtered and washed with H_2O and CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to yield yellow oil (1.82g, 90%), which was taken to the next step coupling reaction.

A solution of *t*-butyl ester bromide (3.54g, 7.55 mmol) in THF (20 mL), precooled to -65°C, was added n-BuLi (1.6 M, 5.0 mL, 8.0 mmol). The resulting purple solution was allowed to stirred at -65°C for 30 min and then cannulated into a solution of aldehyde (1.82g, 7.51 mmol) in THF (20 mL) at -65°C. The mixture was stirred at -50°C for 10 min and warmed up to 0°C and to room temperature H_2O was added to quench the reaction, which then was diluted with EtOAc (200 mL) and washed with 1N HCl and brine. The crude product, after drying and concentration, was purified on a silica gel column eluting with 4:1/Hexane:EtOAc to give pure product (690mg, 15%).

The carbinol (690 mg, 1.09 mmol) was dissolved in acetone and treated with Jones reagent (ca. 2mL) at 5°C until the color of the reaction remained essentially the same color as the Jones reagent. The reaction was then stirred at room temperature for 1 hr. Acetone was removed *in vacuo* and residue was taken into EtOAc, washed with 3N NaOH and brine, dried over Na_2SO_4, and concentrated. The pure product, white oily solid, was obtained from flash chromatography eluting with 85:15/Hexane:EtOAc (420mg, 61%).

The t-butyl ester of the benzophenone (420 mg) was suspended in 5% KOH of $MeOH-H_2O$ (9:1) solution and heated to complete dissolution. The mixture was then stirred at room temperature for 2 hr. 1N HCl (50mL) and EtOAc (200mL) were added. The organic lager was dried over Na_2SO_4 and concentrated to yield a yellow oil. Recrystallization in Hexane-EtOAc yielded beige powder (84%).

To a solution of the benzophenone acid (150 mg, 0.261 mmol) in CH_2Cl_2 (3mL) was added cat. DMF and oxalyl chloride (2.0 M solution in CH_2Cl_2, 250 μL, 0.5 mmol) at room temperature The mixture was stirred at room temperature for 1hr. Solvents were removed and the acid chloride residue was taken into CH_2Cl_2

(5mL) after drying over vacuum for 1 hr.

The solution of azepine alcohol (112 mg, 0.26 mmol), Et_3N (180 μL, 1.3 mmol) and DMAP (37.0 mg, 0.3 mmol) in CH_2Cl_2 (5mL) was treated with the freshly made acid chloride-CH_2Cl_2 solution at 5°C. The reaction mixture was allowed to stir at room temperature for 3 hr and then chromatographed on silica gel eluting with 2:1 / hexane:EtOAc. The product was obtained as white foam solid (60 mg, 22%) (COMPOUND 613).

The Compound 613 (60 mg, 0.061 mmol) was dissolved in THF (7mL) and treated with a drop of TFA and $Pd(OH)_2/C$ (20mg, 30% by weight). The mixture was subjected to hydrogenolysis with a H_2 balloon overnight. THF was removed *in vacuo* and the residue taken into MeOH. The MeOH solution was concentrated after filtering through a pad of celite and chromatographed on 21 x 300 mm C18 column (solvent A: 95:5 water/acetonitrile 0.1% TFA; solvent B:100% acetonitrile; gradient: 0-100% B over 60 min, flow: 15 mL/min). The pure fractions was evaporated to give yellow solids (11 mg, 30%) (COMPOUND 527). m.p. 159-161 (dec)°C; 1H nmr (CD_3OD) δ 7.63 (d, J = 8.7Hz, 2H, ArH), 7.31 (t, J = 7.9 and 8.7Hz, 1H, ArH), 6.92 (s, 2H, ArH), 6.78 (d, J = 8.8Hz, 2H, ArH), 6.50 (d, J = 7.9Hz, 1H, ArH), 6.39 (d, J = 8.7Hz, 1H, ArH), 5.40 (m, 1H, H-4), 4.50 m, 1H, H-3), 3.45 (d, br, 2H, H-7 or H-2), 3.37 (s, 3H, OCH_3), 2.30 and 2.08 (m and m, 1H and 3H, H-5 and H-6); IR (KBr) cm^{-1} 3398, 1705, 1676, and 1614. Anal. Calcd. for $C_{28}H_{28}N_2O_8 \circ 1.0CH_3OH \circ 2.0TFA$: C, 49.76; H, 4.30; N, 3.52. Found: C, 49.98; H, 4.52; N, 3.34. LRFAB (M + 1) : 537.

(±)-*Anti*-3-(4-hydroxy)benzamido-4-[3,5-dihydroxy-4-(1-hydroxy-2- naphthylcarbonyl)]benzoyloxyazepine trifluoroacetic acid salt (COMPOUND 522)

To (±)-*anti*-3-(4-benzyloxy)benzamido-4-[3,5-dibenzyloxy-4-(1 -benzyloxy-2-naphthylcarbonyl)]benzoyloxy-N-benzylazepine (171 mg, 0.170 mmol) dissolved in 2:5 ethyl acetate : ethanol (7 mL) under an atmosphere of nitrogen was added trifluoracetic acid (24 μL, 0.340 mmol) followed by Pearlman's catalyst (34 mg, 20% by wt, 20% by wt on carbon)

introduced an atmosphere of hydrogen and allowed to stir for 37 h. The catalyst was removed by filtration and the volatiles were removed under reduced pressure. The product was chromatographed on a Dynamax®-60 C18 column (41.4 mm ID X 30 cm length) using a linear gradient from 75 : 25 A (0.1% TFA and 5% acetonitrile in water) : B (pure acetonitrile) to pure B over 60 m at 25 mL/min. The product elutes in 22 minutes. Removal of the volatiles under reduced pressure provided Compound 522 as a white solid (34 mg, 25%), mp 134-137°C. IR KBr (disc) cm^{-1} 3397, 3083, 2876, 2815, 2699, 1796, 1776, 1680, 1633, 1607, 1563, 1543, 1506, 1461, 1425, 1386, 1358, 1273, 1236, 1204, 993, 923, 879, 846, 800. Anal. Calcd for $C_{31}H_{28}N_2O_8 \cdot 2CF_3CO_2H \cdot 0.25\ H_2O$: C, 53.27; H, 3.90; N, 3.55. Found: C, 53.42; H, 4.28; N, 3.68.

(±)-*Anti*-3-(4-benzyloxy)benzamido-4-[3,5-dibenzyloxy-4-(1-benzyloxy-2-naphthylcarbonyl)]benzoyloxy-N-benzylazepine (COMPOUND 607)

To a solution of 3,5-dibenzyloxy-4-(1-hydroxy-2-naphthylcarbonyl)benzoic acid (203 mg, 0.341 mmol, 467-29-A) in anhydrous dichloromethane (5 mL) under an atmosphere of nitrogen at 0°C was added oxalyl chloride (256 µL, 0.512 mmol, 2 M in dichloromethane) dropwise over 5 minutes followed by anhydrous dimethylformamide (3 drops). The ice bath was removed and the reaction mixture was allowed to stir for 3 h at room temperature. The volatiles were removed under reduced pressure and the remaining solid was dried under vacuum for 3 h.

To a solution of (±)-*anti*-3-(4-benzyloxy)benzamido-4-hydroxyazepine (147 mg, 0.341 mmol), triethylamine (143 uL, 1.02 mmol), and dimethylaminopyridine (4.2 mg, 0.0341 mmol) in anhydrous dichloromethane (8 mL) under an atmosphere of nitrogen at 0°C was added a solution of the above generated acid chloride in anhydrous dichloromethane (8 mL) dropwise over 0.5 h. After allowing to stir while warming to room temperature overnight the reaction mixture was diluted with dichloromethane (100 mL) and washed with water (50 mL). The

dichloromethane layer was dried over magnesium sulfate, filtered, and the volatiles were removed under reduced pressure to give a crude white solid. The solid was purified using flash column chromatography (silica gel, 9:1 hexane: ethyl acetate - 2:1 hexane : ethyl acetate) to provide Compound 607 as a white solid (175 mg, 51%).

3,5-Dibenzyloxy-4-(1-benzyloxy-2-naphthylcarbonyl)benzoicacid

To a solution of t-butyl 3,5-dibenzyloxy-4-(1-benzyloxy-2-naphthylcarbonyl)benzoate (481 mg, 0.715 mmol) in methanol (75 mL) was added 10N NaOH (15 mL). The reaction mixture was heated at 50°C for 2 h. The volatiles were removed under reduced pressure. The reaction mixture was acidified with 6 N HCl and extracted with ethyl acetate (1 X 400 mL). The ethyl acetate layer was dried over anhydrous magnesium sulfate, filtered, and the volatiles were removed under reduced pressure. The product was chromatographed on a Dynamax®-60 C18 column (41.4 mm ID X 30 cm length) using a linear gradient from 100% A (5% acetonitrile in water) to 100% B (pure acetonitrile) over 120 m at 25 mL/min. The product elutes in 110 minutes. Removal of the volatiles under reduced pressure provided the title compound as a white solid (210 mg, 49%).

t-Butyl 3,5-dibenzyloxy-4-(1-hydroxy-2-naphthylcarbonyl) benzoate

To a solution of 1-benzyloxy-2-naphthoic acid (237 mg, 0.852 mmol) in anhydrous dichloromethane (5 mL) under an atmosphere of nitrogen at 0°C was added oxalyl chloride (80 μL, 0.920 mmol, 2M in dichloromethane) dropwise over 0.5 h. The reaction mixture was allowed to stir while warming to room temperature overnight. The volatiles were removed under reduced pressure and the residual solid was dried under vacuum for 1 h.

To a solution of t-butyl 3,5-dibenzyloxy-4-bromobenzoate (400 mg, 0.852 mmol) dissolved in anhydrous tetrahydrofuran (4 mL) under an atmosphere of nitrogen with an internal temperature of -78°C (ether / dry ice) was added n-

butyllithium (590 μL, 0.937 mmol, 1.6 M in hexanes) dropwise at a rate which did not allow the internal temperature to rise above -65°C. To the reaction mixture was added a solution of the above generated acid chloride in anhydrous tetrahydrofuran (4.5 mL) dropwise at a rate which did not allow the internal temperature to rise above -65°C. The reaction mixture was allowed to stir while warming to room temperature over 2 h. The reaction mixture was quenched with solid ammonium chloride and the volatiles were removed under reduced pressure. The crude residue was diluted with ethyl acetate (400 mL) and washed with 0.5N HCl (100 mL). The ethyl acetate layer was dried over anhydrous magnesium sulfate, filtered, and the volatiles were removed under reduced pressure. The crude residue was purified using flash column chromatography (silica gel, 5% ethyl acetate / hexane - 10 % ethyl acetate / hexane) which provided a white solid of the title compound (96 mg, 34%).

1-Benzyloxy-2-naphthoic acid

To a solution of benzyl 1-benzyloxy-2-naphthoate (7.38 g, 20.0 mmol), in methanol (10 mL) was added 10N NaOH (20 mL). The reaction mixture was placed in an oil bath at 70°C for 3 h. The reaction mixture was acidified with 3N HCl and the solid was collected by suction filtration. The crude product was recrystallized from methanol / H_2O to provide a white solid of the title compound (5.20 g, 93%) mp 132-133°C. IR KBr (disc) cm^{-1} 3028, 2874, 1701, 1625, 1566, 1501, 1457, 1411, 1364, 1333, 1286, 1248, 1210, 1166, 1145, 1084, 1029, 980, 911, 825, 795, 769, 727, 624. Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.80; H, 5.09.

Benzyl 1-benzyloxy-2-naphthoate

To a soluton of 1-hydroxy-2-naphthoic acid (3.00 g, 15.9 mmol) in anhydrous dimethylformamide (60 mL) under an atmosphere of nitrogen was added anhydrous potassium carbonate (4.88 g, 35.1 mmol) followed by the dropwise addition of benzyl bromide (4.75 mL, 39.9 mmol) over 0.25 h. The reaction mixture

was allowed to stir for 3 h at room temperature. The reaction mixture was quenched by the dropwise addition of H_2O. After removing a small amount of insoluble material by filtration, the crude product was partitioned between ethyl acetate (200 mL) and H_2O (50 mL). The ethyl acetate layer was dried over anhydrous magnesium sulfate, filtered, and the volatiles were removed under reduced pressure to provide a white solid of the title compound (6.31 g, 107%, of sufficient purity for the next step).

Anti-4-(4-(2-Carboxy-6-hydroxybenzoyl)-3,5 dihydroxybenzoylamino)hexahydro-3-(4-hydroxybenzoylamino) azepine, trifluoroacetic acid salt (COMPOUND 515)

Hexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepin-4-one

A 25 mL 3-neck round bottom flask under nitrogen was charged with 2.0 N oxalyl chloride/methylene chloride (Aldrich, 1.125 mL, 2.25 mmol), diluted with anhydrous methylene chloride (2 mL), cooled (-65°C), and treated dropwise with anhydrous dimethylsulfoxide (0.35 g, 4.5 mmol) in anhydrous methylene chloride (1.2 mL) at a rate to keep the pot temperature below -60°C. The mixture was stirred at -65±5°C for 30 min, then treated dropwise with a solution of *syn*-hexahydro-4-hydroxy-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.645 g, 1.5 mmol) in anhydrous methylene chloride (1.5 mL) at a rate to keep the pot temperature below -55°C. The mixture was stirred at -55±5°C for 2 h, then treated dropwise with triethylamine (1.5 mL), warmed to room temperature over one hour, and diluted with methylene chloride (10 mL). The organic solution was washed with water (10 mL), saturated aqueous sodium bicarbonate (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed on silica gel (eluted with 5% acetone/methylene chloride) to afford hexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepin-4-one (0.53 g, 82%) as a viscous colorless oil.

H xahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepin-4-one, xime

A solution of hexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepin-4-one (0.87 g, 2.03 mmol) in ethanol (12 mL) was treated with hydroxylamine hydrochloride (0.19 g, 2.73 mmol), followed by 25% methanolic sodium methoxide (Aldrich, 0.20 g, 0.93 mmol), and was heated to 50°C for one hour. The mixture was cooled to room temperature and treated with additional 25% methanolic sodium methoxide (0.42 g, 1.94 mmol), then concentrated *in vacuo* to afford hexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepin-4-one oxime (0.89 g, 99%) as a colorless foam.

***Anti*-4-(3,5-Bis(phenylmethoxy)-4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)benzoylaminohexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (Compound 614)**

A solution of hexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepin-4-one oxime (0.40 g, 0.90 mmol) in reagent methanol (25 mL) in a Parr bottle was treated with Raney Nickel (Aldrich, quarter tsp.), then subjected to hydrogenation at 49-50 psi for six hours. The solution was carefully evacuated of hydrogen, filtered through celite, and the filtrate was concentrated *in vacuo* to afford 4-aminohexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine, 1:1 mixture of isomers, which was kept under nitrogen. Meanwhile, 2'-carbobenzyloxy-2,6,6'-tribenzyloxybenzophenone-4-carboxylic acid (0.37 g, 0.55 mmol) was placed in a round-bottom flask and repeatedly covered with toluene and concentrated *in vacuo* to remove all water and other persistent solvents. Finally, the residue was dissolved in anhydrous methylene chloride (2 mL) under nitrogen, treated with dimethylformamide (3 drops), then with 2.0N oxalyl chloride/methylene chloride (0.4 mL, 0.8 mmol), and stirred at room temperature for one hour. The solution was concentrated *in vacuo*, placed under high vacuum for one hour, then dissolved in methylene chloride (3 mL) and added to the 4-aminohexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepineprepared

above. Sodium hydroxide (1.0N, 1.5 mL) was added, and the mixture was stirred for one hour and separated. The aqueous layer was extracted with methylene chloride (2 x 10 mL), and the combined organic layer and extracts were washed with saturated sodium chloride (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed (flash) on silica gel (eluted successively with 3% acetone/methylene chloride, 5% acetone/methylene chloride, and 8% acetone/methylene chloride) to afford, initially, *syn*-4-(3,5-bis(phenylmethoxy)4-(2-carbophenymethoxy-6-phenylmethoxybenzoyl)benzoylaminohexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.26 g, 43%), then *anti*-4-(3,5-bis(phenylmethoxy)-4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl) benzoylaminohexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.21 g, 35%) (COMPOUND 614) as colorless foams. The combined yield was 0.47 g (78%).

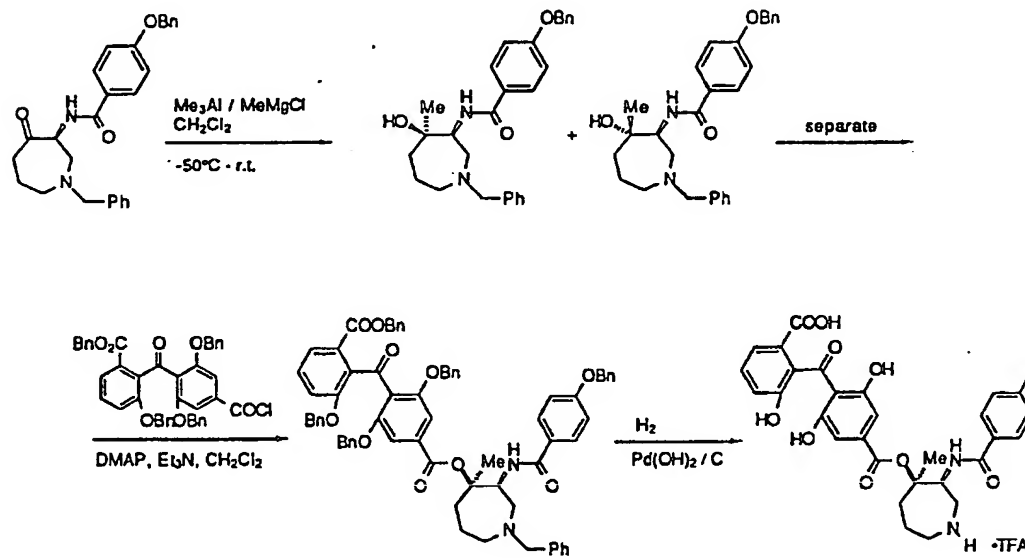
Anti-4-(4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyl-amino)hexahydro-3-(4-hydroxybenzoylamino)azepine, trifluoroacetic acid salt (Compound 515)

A solution of *anti*-4-(3,5-bis(phenylmethoxy)-4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)benzoylaminohexahydro-3-(4- phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.20 g, 0.183 mmol) in reagent ethanol (9 mL) and ethyl acetate (1 mL) in a 2-neck 25-mL round bottom flask under nitrogen was treated with Pearlman's catalyst (20% $Pd(OH)_2/C$, 50 mg) and trifluoroacetic acid (42 mg, .37 mmol). The flask was fitted with a balloon and a balloon valve, purged with hydrogen, and placed under positive hydrogen pressure for 22 h, then evacuated of hydrogen and purged for several minutes with nitrogen. The solution was carefully filtered through celite (wash filter pad with ethanol) and the filtrate was concentrated *in vacuo* to a yellow foam. This was dissolved in a small amount of dimethylformamide and loaded onto a C_{18} HPLC column. Gradient elution (5% $MeCN/H_2O/0.1\%$ TFA to 50% $MeCN/H_2O/0.4\%$ TFA over one hour) followed by freeze drying

afforded *anti*-4-(4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoylamino)hexahydro-3-(4-hydroxybenzoylamino) azepine, trifluoroacetic acid salt (80 mg, 60%) (compound 515) as a voluminous yellow solid: mp >300°C(dec); R_f (4% acetic acid/ethanol) 0.45; IR (KBr) 1680, 1635, 1607 cm^{-1}; ^1H NMR (d_6-DMSO) δ 11.61 (s, 2H), 10.00 - 10.10 (br s, 1H), 9.85 (s, 1H), 8.80 - 9.05 (br s, 2H), 8.60 (d, 1H, J = 7 Hz), 8.26 (d, 1H, J = 7 Hz), 7.63 (d, 2H, J = 9 Hz), 7.36 (d, 1H, J = 8Hz), 7.26 (t, 1H, J = 8Hz), 7.05 (d, 1H, J = 8Hz), 6.79 (d, 2H, J = 9Hz), 6.61 (s, 2H), 4.15 - 4.35 (m, 2H), 3.15 - 3.40 (m, 3H), 2.95 - 3.15 (m, 1H), 1.70 - 2.05 (m, 4H). Anal. Calcd. for $C_{28}H_{27}N_3O_9$ • 1.3($C_2HO_2F_3$) • 2.0(H_2O): C, 50.09; H, 4.44; N, 5.73. Found: C, 49.82; H, 4.53; N, 5.69.

(Compound 598)

syn-4-[4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-N-hydroxybenzamido)-4-methylazepin triflu roacetic acid.



659 598

syn-4-hydroxy-3-(4-benzyloxybenzamido)-4-methylazepine.

To a 250 mL 3-neck round-bottom flask equipped with a thermometer under N_2 was added trimethylaluminum (18 mmol, 9.0 mL, 2M solution in toluene). This was cooled to 5°C in an ice/water bath and methylmagnesium chloride (13.5 mmol, 4.5 mL, 3M solution in THF) was added. This mixture was cooled to -50°C in a dry ice/acetone bath. To a separate flask was added N-benzyl-3-(4-benzyloxybenzamido)-4-azepine (1.07 mmol, 460 mg) and 30 mL anhydrous CH_2Cl_2. This was cooled to 0° C and added dropwise *via* cannula to the $(CH_3)AlMgCl$ solution. The cloudy reaction mixture was allowed to stir under N_2 and slowly warm to room temperature where it became homogeneous. After 20 hours, acetone (4 mL) was added, the reaction was cooled in an ice/water bath and 5% $NaHCO_3$ (30 mL) was added slowly. The

resulting emulsion was filtered through Celite, the layers separated and the aqueous layer extracted with CH_2Cl_2. The organic layers were dried and concentrated *in vacuo* to yield a mixture of diastereomeric products. Separation *via* flash column chromatography yielded the *syn* (81 mg, 17% yield) and anti (112 mg, 24% yield) products.

syn-N-Benzyl-4-[4-(2-benzyloxycarbonyl-6-benzyloxybenzoyl)-3,5-dibenzyloxy]-3-(4-benzyloxybenzamido)-4-methylazepine. (Compound 659)

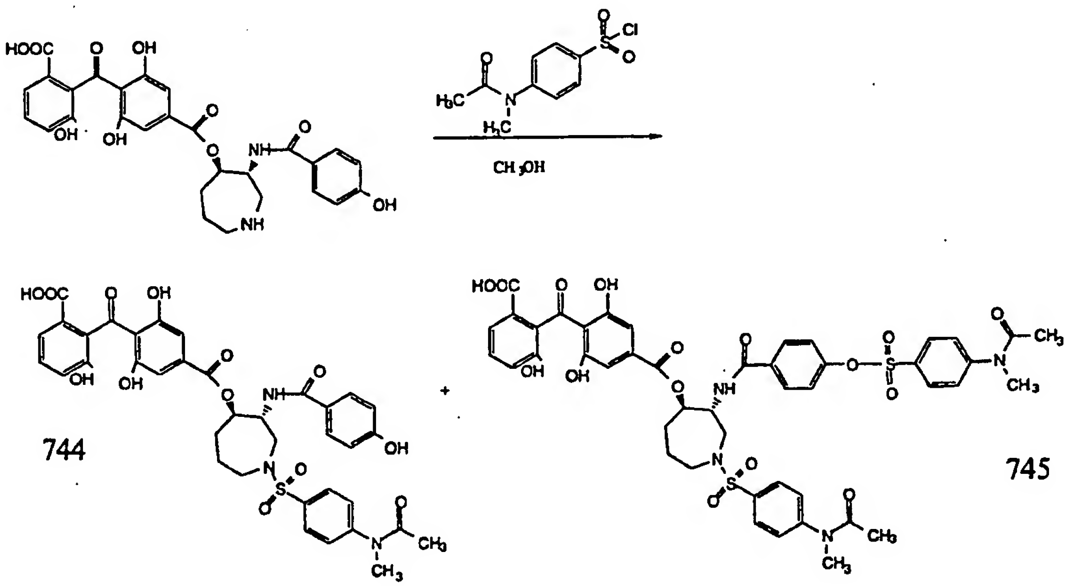
To a dry 25 mL round-bottom flask under N_2 was added 4-[4-(2-benzyloxy-6-(benzyloxycarbonyl)benzoyl]-3,5-dibenzyloxybenzoic acid (0.50 mmol, 338 mg) and 5 mL anhydrous CH_2Cl_2. After cooling to 0° C oxalyl chloride (0.75 mmol, 0.07 mL) then DMF (2 drops) were added. This was allowed to stir for 1 hour while warming to room temperature. Monitoring by TLC (solvent system: 2:1 Hexanes: EtOAc) indicated complete formation of the acid chloride. The solvent was removed *in vacuo* to yield the acid chloride as an orange/brown oil.

To a 50 mL round-bottom flask under N_2 was added syn-4-hydroxy-3-(4-benzyloxybenzamido)-4-methylazepine (0.32 mmol, 144 mg) in 4 ml anhydrous CH_2Cl_2. This was followed by addition of DMAP (tip of spatula) and triethylamine (1.44 mmol, 0.2 ml). A solution of the acid chloride (generated above) in 4 ml CH_2Cl_2 was added and the mixture stirred for 22 hours at room temperature. The reaction was diluted with CH_2Cl_2, washed with 0.5 N NaOH (turned cloudy), dried and concentrated *in vacuo*. Purification *via* flash column (solvent: 5 - 20 % acetone in CH_2Cl_2) yielded Compound 659 (50 mg, 14% yield) plus recovered starting azepine meterial (120 mg, 84%).

syn-4-[4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)-4-methylazepine trifluoroacetic acid. (Comp und 598)

To a 25 mL 3-neck round-bottom flask under N_2 was added syn-N-benzyl-4-[4-(2-benzyloxycarbonyl-6-benzyloxybenzoyl)-3,5-dibenzyloxy]-3-(4-benzyloxybenzamido)-4-methylazepine (0.05 mmol, 50 mg), 3 mL ethanol and 1 mL ethyl acetate.
To this was added trifluoroacetic acid (0.13 mmol, 10μL then 20% $Pd(OH)_2/C$ (40 mg). Immediately following the addition of 20% $Pd(OH)_2/C$, H_2 was introduced at 1 atmosphere. The reaction stirred at room temperature under 1 atm H_2 for 24 hours. TLC indicated a complete reaction (solvent system: 8:1:1, butanol : water: acetic acid). The reaction was flushed with N_2, then filtered through Celite and concentrated. After purification by HPLC (21 mm C18 column, gradient %B = 0 to 50 over 60 min. where A = 0.1% TFA, 5% CH_3CN in water and B = CH_3CN, 15 mL/min., UV = 254 nm) Compound 598 (4.5 mg, 13% yield) was isolated as a yellow powder. m.p. dec. 165° C; ^1H NMR (CD_3OD) δ 7.70 (d, 2H), 7.49 (d, 1H), 7.26 (t, 1H), 7.00 (d, 1H), 6.85 (m, 4H), 5.16 (m, 1H), 3.43 (m, 3H), 3.18 (m, 2H), 2.80 (m, 1H), 2.20 (m, 3H), 1.72 (s, 3H); HRMS (m/z) (M + 1) calcd for $C_{29}H_{29}N_2O_{10}$ 565.18222, found 565.18341.

(±)-trans-4-[4-(2-Carboxy-6-hydr xybenzoyl)-3,5-dihydroxybenzoyl xy]-3-[4-(4-N-methylacetamidobenzene sulfonyloxy)b nzamido]-1-(4-N-methylacetamido benzensulfonyl)perhydroazepine (Compound 745) and (±)-trans-4-[4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-[4-hydroxybenzamido]-1-(4-N-methylacetamido benzensulfonyl)perhydroazepine (Compound 744)



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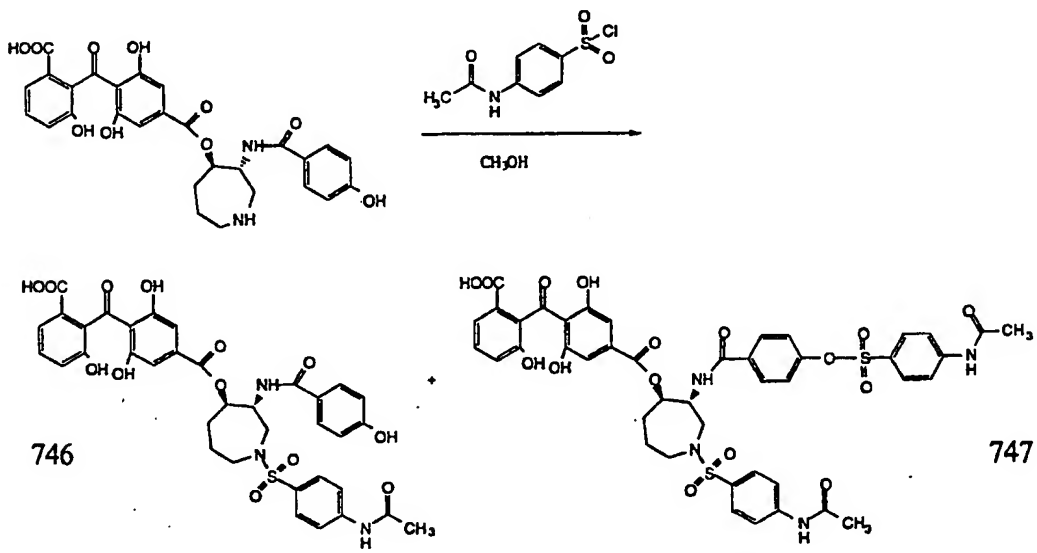
745

To a solution of the Balanol (200 mg, 0.366 mmol) in methanol (2 ml) was added N-methyl-4-acetamidobenzenesulfonylchloride (135 mg, 0.55 mmol) in 1 ml of methanol. The mixture was stirred at room temperature for 24 hr. The solvents were removed under vacuum and the resulting yellow residue was purified by HPLC (21 X 250 mm C18 column; A: 5% CH_3CN in H_2O + 0.1% TFA, B: 100% CH_3CN; 0-100 B over 1 h) to give 42 mg (14%) of (Compound 744) as a light yellow powder. m.p. 210-213 °C dec. Anal. Calcd for $C_{37}H_{35}N_3O_{13}S \cdot 1.0CH_3OH$: C, 56.22; H, 5.09; N, 5.18; S, 3.95. Found: C, 56.03; H, 4.66; N, 5.39; S, 3.94 and 18 mg (5%) of (Compund 745) as a light yellow powder. m.p. 184-186 °C dec. Anal. Calcd for $C_{46}H_{44}N_4O_{16}S_2 \cdot 2.0H_2O$: C, 54.76;

H, 4.79; N, 5.55; S, 6.35. Found: C, 54.19; H, 4.40; N, 5.33; S, 6.15.

(±)-trans-4-[4-(2-Carb xy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-[4-(4-acetamid benzenesulf nyloxy)b nzamido]-1-(4-acetamidobenzenesulfonyl)perhydroazepine (Compund 747) and (±)-trans-4-[4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-[4-hydroxybenzamido]-1-(4-acetamidobenzenesulfonyl)perhydroazepine (Compound 746)



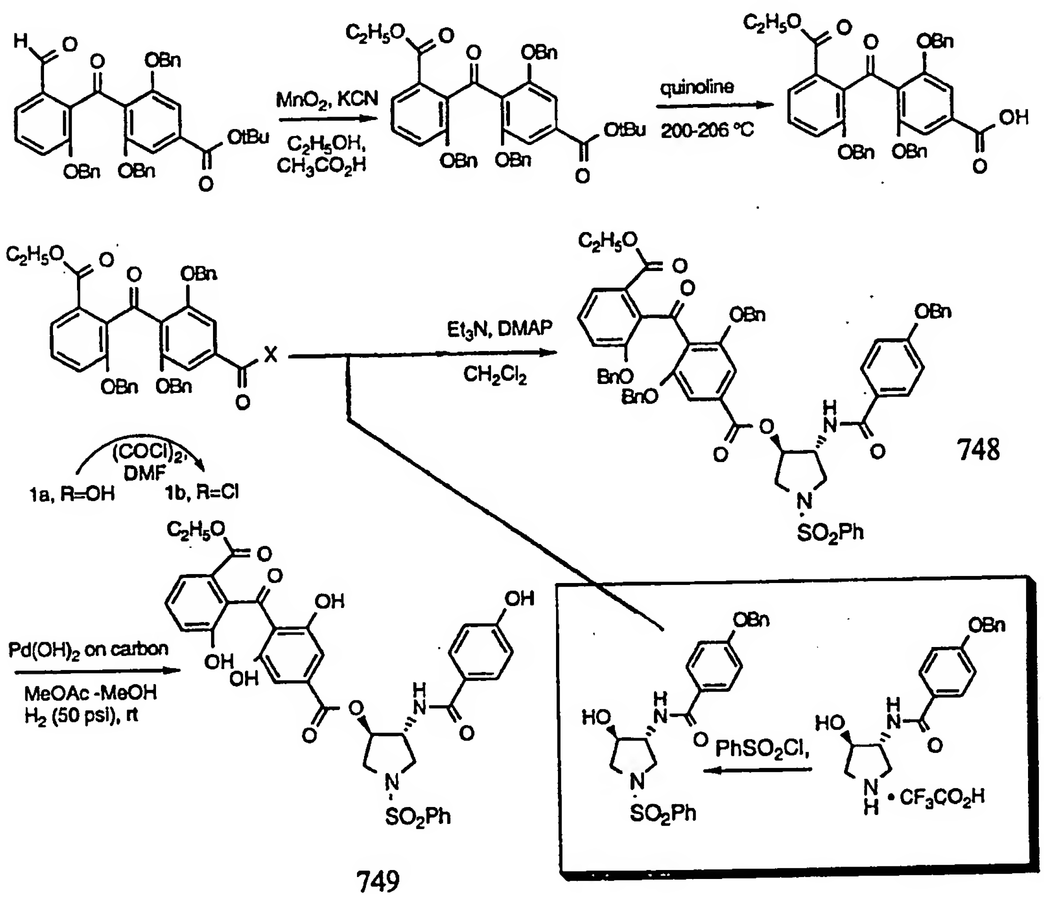
746

747

To a solution the benzamido azepine (200 mg, 0.366 mmol) in methanol (2 ml) was added 4-acetamidobenzenesulfonylchloride (126 mg, 0.55 mmol) in 1 ml of methanol. The mixture was stirred at room temperature for 24 hr. The solvents were removed under vacuum and the resulting yellow residue was purified by HPLC (21 X 250 mm C18 column; A: 5% CH_3CN in H_2O + 0.1% TFA, B: 100% CH_3CN; 0-100 B over 1 h) to give 35 mg (12%) of Compound 746 as a light yellow powder. m.p. 210-213 °C dec. Anal. Calcd for $C_{36}H_{33}N_3O_{13}S \cdot 1.0CH_3OH$: C, 55.70; H, 4.93; N, 5.27; S, 4.02. Found: C, 55.38; H, 4.46; N, 5.30; S, 3.93 and 14 mg (4%) of Compound 747 as a light yellow powder. m.p. 222-225 °C dec. Anal. Calcd for $C_{44}H_{40}N_4O_{16}S_2 \cdot 3.0H_2O$: C, 52.90; H,

4.64; N, 5.61; S, 6.42. Found: C, 52.93; H, 4.21; N, 5.45; S, 6.03.

(±)-*anti*-1-Phenylsulfonyl-4-[4-(2-ethoxycarbonyl-6-hydroxybenz yl-3,5-dihydroxybenzoyloxy]-3-(4-hydr xybenzamido)-pyrrolidine (C mpound 749)



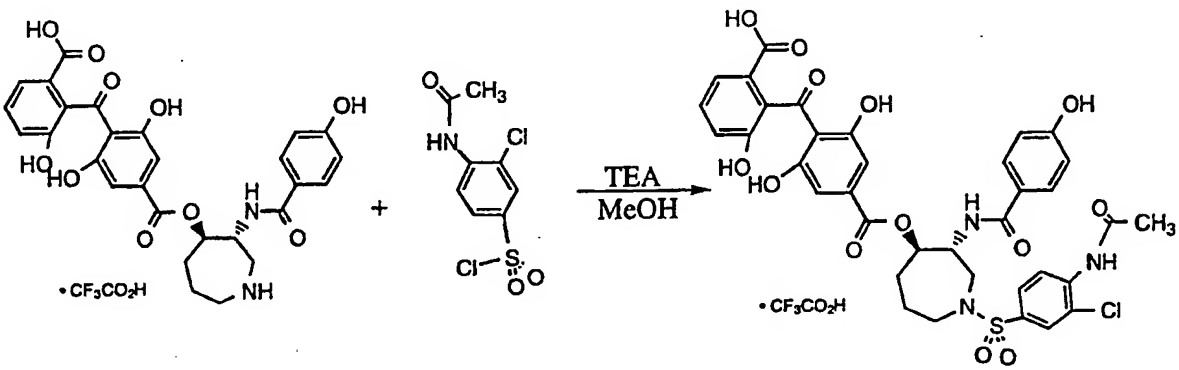
To a stirred biphasic solution of amine hydrochloride (1.18 mmol, 500 mg) in methylene dichloride/water (30 mL/30 mL), was added sodium bicarbonate ($NaHCO_3$, 3.90 mmol, 413 mg) and benzenesulfonyl chloride (1.70 mmol, 300 mg), respectively. The mixture was stirred at room temperature for 18 hours and diluted with methylene chloride (150 mL) and saturated sodium

bicarbonate solution (50 mL). The layers were separated and the aqueous layer re-extracted with methylene chloride (50 mL). The combined organic layers were then washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The hydroxyamide was triturated from chloroform/hexane and isolated in 84% purified yield (460 mg) as a white solid. To a stirred solution of aldehyde (1.30 mmol, 800 mg) in ethanol (absolute, 75 mL) was added potassium cyanide (KCN, 8.12 mmol, 530 mg), glacial acetic acid (2.60 mmol, 156 mg), and manganese(II) oxide (MnO_2 (activated) 13.0 mmol, 1.13g). The mixture was stirred at room temperature for 36 hours under nitrogen atmosphere, diluted with ethanol (100 mL), and filtered over a pad of Celite. The Celite pad was washed with ethanol (50 mL), the ethanol evaporated *in vacuo*, and the resulting yellow solid partitioned between chloroform (200 mL) and water (100 mL). The layers were separated, the aqueous layer was re-extracted with chloroform (50 mL), and the combined organic layers were washed with 10% HCl (Note 1: perform the acid wash in a well ventilated area, potential source of hydrogen cyanide), saturated sodium bicarbonate solution, brine, dried over anhydrous sodium sulfate, filtered and the solvent evaporated under reduced pressure. The bisester was isolated (830 mg) as a yellow solid in >95% yield and used without purification. The bisester (1.44 mmol, 950 mg) was dissolved in quinoline (freshly distilled, 10 mL) and placed in an oven-dried, 24 mL single-necked, round bottomed flask under a nitrogen atmosphere. The reaction flask was then lowered into a preheated oil bath (205 °C), and the reaction was stirred at 200-206 °C for 3 hours (monitored by TLC). The dark brown solution was allowed to cool to room temperature, diluted with dichloromethane (CH_2Cl_2, 200 mL) and 10% HCl solution (50 mL), and the organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and the solvent removed *in vacuo*. The benzophenone acid was purified *via* flash column chromatography and isolated as a light brown solid 420 mg) in 48% yield. To a chilled (ice/water bath) and stirred solution of the benzophenone acid (0.31 mmol, 185 mg) in

methylene chloride (5 mL) under a nitrogen atmosphere was added oxalyl chloride ($(COCl)_2$, 0.46 mmol, 60 mg), and N,N-dimethylformamide (DMF, catalytic, 2 drops), and the red solution was stirred under the above conditions for 3 hours. The resulting acid chloride was then concentrated *in vacuo* and stored at reduced pressure until needed. In a separate flask, the alcohol (0.37 mmol, 170 mg) was added to methylene chloride (5 mL), and the suspension stirred at room temperature under a nitrogen atmosphere. Triethylamine (Et_3N, 0.92 mmol, 93 mg) and 4-dimethylaminopyridine (DMAP, catalytic, ≈ 2-3 mg) were added. A solution of the acid chloride (see above) in methylene chloride (5 mL) was then slowly added (*via* syringe), and the resulting deep red solution was stirred at room temperature over night (15-18 hours). The deep-red solution was transferred to a separatory funnel, diluted with methylene chloride (200 mL), and washed with saturated sodium bicarbonate solution. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting red foam was chromatographed on a silica column (2:1:1 hexane:ethyl acetate:methylene chloride) and perbenzylated intermediate (Compound 748) was isolated (140 mg, 43% yield, purified) as a yellow solid. Perbenzylated intermediate (0.12 mmol, 130 mg) was dissolved in ethyl acetate (15 mL) and placed in a Parr shaker bottle. Ethanol (5 mL), and Pearlman's catalyst ($Pd(OH)_2$ on carbon, 20% palladium by weight, 100 mg) were then added, and the mixture was shaken on the Parr hydrogenator at 50 psi of hydrogen atmosphere for 4 hours at room temperature (reaction monitored by TLC). The reaction mixture was diluted with ethanol (50 mL) and filtered over a pad of Celite, the Celite was washed well with ethanol (50 mL), and the resulting bright yellow solution was concentrated *in vacuo*. The product (Compound 749) was purified *via* HPLC (41 X 300 mm C18 reverse phase column, pump A: 5% acetonitrile in water + 0.1% trifluoroacetic acid; pump B: 100% acetonitrile; 0-100% pump B over 90 minutes, flow rate = 25 mL/min, retention time = 58.1 minutes). The purified fractions were concentrated and the water removed by lyophilization to

give 31 mg (37% purified yield) of the title compound as a bright yellow solid. IR (KBr): 1712, 1681, 1636, 1608, 1544, 1509, 1464, 1449, 1425, 1368, 1337, 1298, 1231, 1203 cm^{-1}. MS (m/e, low resolution FAB): $[M + H]^+ = 691$.

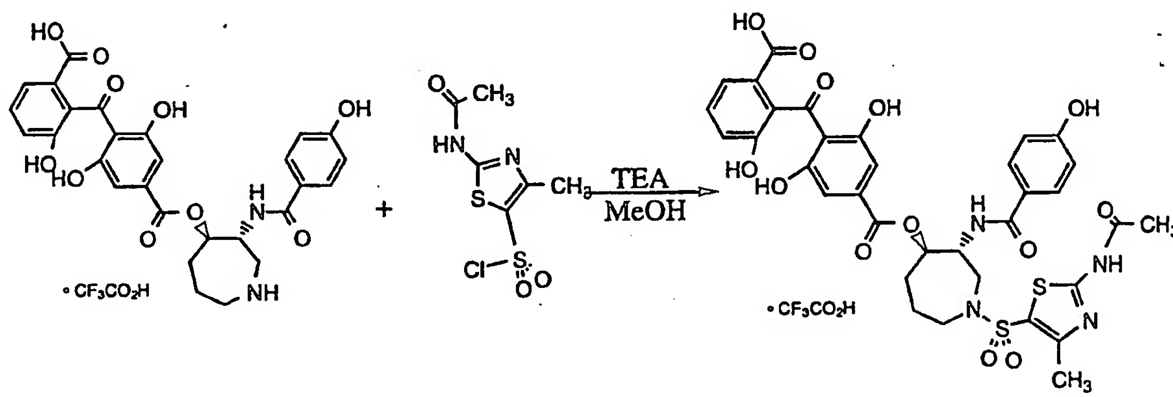
(±)-Trans-4-[4-(2-Hydr xycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydr xybenzamido)-1-(4-ac tamido-3-chlorobenzenesulfonyl)perhydroazepine (Compound 750)



750

Racemic balanol (100 mg, 147 μmol) was dissolved in methanol (1 mL) and treated with triethylamine (204 μL, 147 μmol) and 4-acetamido-3-chlorobenzenesulfonyl chloride (58.92 mg, 219.7 μmol) in methylene chloride (1 mL). After stirring at room temperature for 2 h, the mixture was concentrated under vacuum to a yellow film. The residue was dissolved in DMF (2 mL) and chromatographed on a Dynamax©-60 C_{18} column (41 mm ID X 25 cm length) using a linear gradient from 100% A (0.1% TFA and 5% acetonitrile in water) to 100% B (pure acetonitrile) over 60 m at 25 mL/min. The clean product, which eluted in 37 min, was freeze-dried to give a yellow powder (46 mg, 40%) (Compound 750): m.p. 190° Cdec; ^{1}H-NMR (DMSO, 300 MHz) δ 1.64-1.82 (2H, m), 2.15 (3H, s), 4.27 (1H, pseudo t), 5.11 (1H, pseudo t), 6.75 (4H, t), 7.03 (1H, d, J = 8 Hz), 7.26 (1H, t), 7.33-7.36 (1H, m), 7.64 (2H, d, J = 7 Hz), 7.75 (1H, d, J = 8 Hz), 7.86 (1H, s), 8.10 (1H, d, J = 9 Hz), 8.19 (1H, d, J = 9 Hz), 9.75 (1H, s), 9.84 (1H, s), 9.95 (1H, s), 11.63 (1H, s); IR (KBr): cm^{-1} 3388, 3083, 2949, 2877, 2360, 2340, 1703, 1635, 1607, 1583, 1538, 1509, 1461, 1425, 1382, 1334, 1236, 1203, 1158, 1100, 1061, 994, 919, 869, 848, 764, 673, 619, 582, 561, 440. Anal. Calcd. for $C_{36}H_{32}ClN_3O_{13}S \cdot 1.5H_2O \cdot .25TFA$: C, 52.33; H, 4.24; N, 5.01; S, 3.82. Found: C, 52.57; H, 4.04; N, 5.12; S, 3.47. LRMS (FAB) m/z 782.1 (782.18 calcd for $C_{36}H_{32}ClN_3O_{13}S$).

(±)-Trans-4-[4-(2-Hydroxycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxyb nzoyloxy]-3-(4-hydroxybenzamido)-1-(2-acetamido-4-m thyl-5-thiazolylsulfonyl)perhydroazepine (Comp und 751)

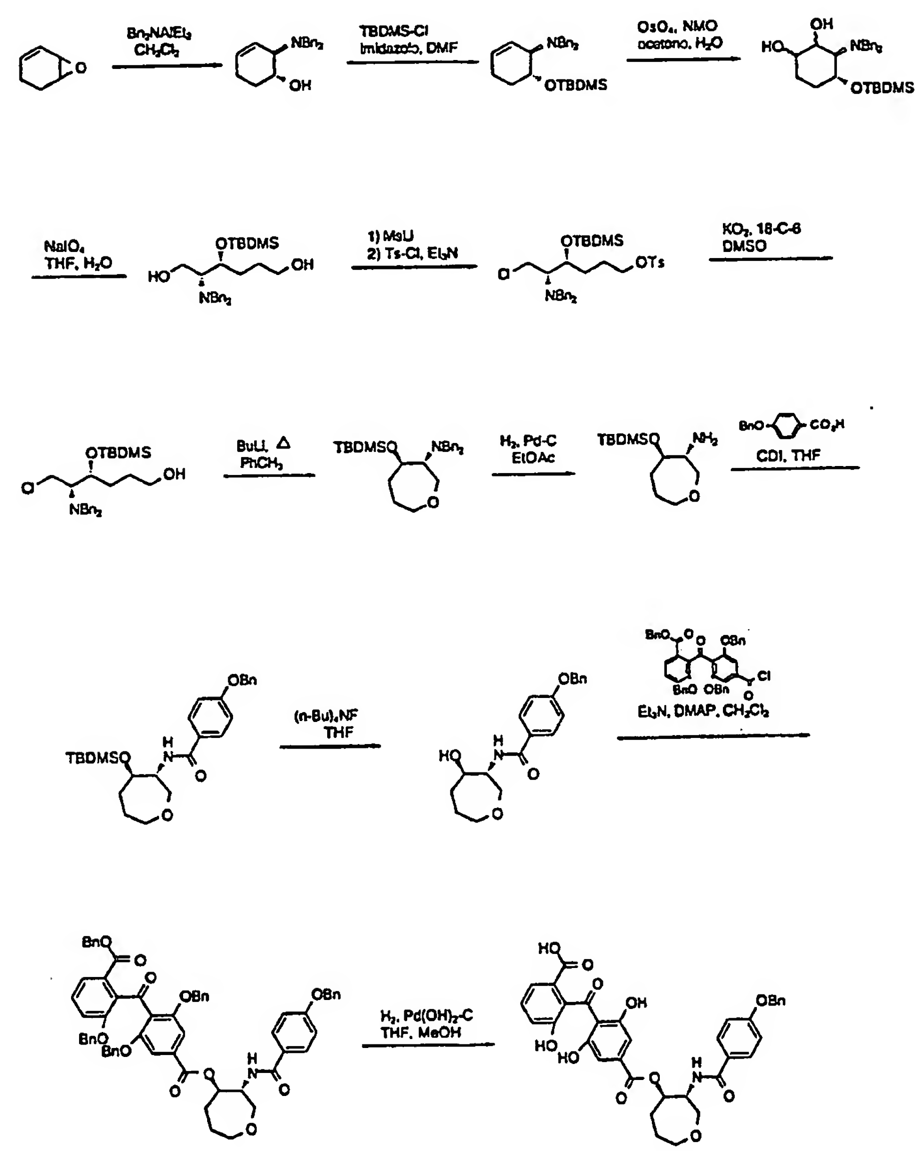


751

Racemic balanol (100 mg, 147 μmol) was dissolved in methanol (1 mL) and treated with triethylamine (204 μL, 147 μmol) and 4-acetamido-4-methyl-5-thiazolesulfonyl chloride (55.97 mg, 219.7 μmol) in methylene chloride (1 mL). After stirring at room temperature for 2 h, the mixture was concentrated under vacuum to a yellow film. The residue was dissolved in DMF (2 mL) and chromatographed on a Dynamax®-60 C_{18} column (41 mm ID X 25 cm length) using a linear gradient from 100% A(0.1% TFA and 5% acetonitrile in water) to 100% B (pure acetonitrile) over 60 m at 25 mL/min. The clean product, which eluted in 35 m, was freeze-dried to give a yellow powder (26 mg, 23%) (Compound 751): m.p. 200°C dec; ^{1}H-NMR (DMSO, 300 MHz) δ 1.75-1.94 (2H, m), 2.01-2.14 (2H, m), 2.23 (3H, s), 4.27-4.36 (1H, m), 5.19 (1H, pseudo t), 6.83 (4H, d, J = 8 Hz), 7.11 (1H, d, J = 8 Hz), 7.35 (1H, t), 7.42 (1H, d, J = 8 Hz), 7.70 (2H, d, J = 8 Hz), 8.28 (1H, d, J = 8 Hz), 9.91 (1H, s), 10.01 (1H, s), 11.69 (1H, s), 12.67 (1H, s); IR (KBr): cm^{-1} 3399, 3273, 3083, 2951, 2360, 2338, 1769, 1700, 1635, 1609, 1541, 1507,

1457, 1427, 1371, 1286, 1237, 1202, 1152, 1101, 1076, 992, 922, 848, 763, 671, 639, 584, 548. Anal. Calcd. for $C_{34}H_{32}N_4O_{13}S$ • $1.5H_2O$ • .5TFA: C, 49.29; H, 4.20; N, 6.57; S, 7.52. Found: C, 49.44; H, 4.14; N, 6.40; S, 7.04. LRMS (FAB) m/z 768.78 (768.78 calcd for $C_{34}H_{32}N_4O_{13}S_2$).

Trans-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-hydroxycarbonyl)benzoyl-3,5-dihydroxybenzoyloxy]perhydrooxepine (C mpound 557)



635 557

Triethylaluminum (40.61 mL, 297 mmol) was added dropwise over 30 min. to a stirred solution of dibenzylamine (58.61 g, 297 mmol) in CH_2Cl_2 (300 mL) at 5°C. The resultant mixture was stirred at room temperature for an additional 30 min., recooled to 5°C, and the epoxide (28.54 g, 297 mmol, for preparation, see: J.K. Crandall, etc., *J. Org. Chem.*, **1968**, 33, 423) in CH_2Cl_2 (100 mL) was added dropwise over 40 min. Stirring was continued for 30 min. at 5°C and 16 h at room temperature. Aq. 5N NaOH (300 mL) was added cautiously *via* an addition funnel over 1h while the mixture was cooled with an ice bath. The cooling bath was removed and stirring was continued at room temperature for 3h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 X 50 mL). The combined organic phases were washed with H_2O (2 X 300 mL) and brine (2 X 300 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (SiO_2, Et_2O: hexane = 1 : 15 followed by Et_2O: hexane = 1 : 7) to give a colorless oil (49.63 g, 57%). To a cold solution (ice-H_2O bath) of the colorless oil from the preceding reaction (40.24 g, 137 mmol) and imidazole (14.02 g, 206 mmol) in DMF was added TBDMS-Cl (20.69 g, 137 mmol) in several portions over 5 min. The resultant solution was stirred at room temperature for 16h, poured into Et_2O (600 mL) and washed with H_2O (5 X 200 mL). The organic layer was dried ($MgSO_4$) and evaporated to give a colorless oil (54.57 g, 98%). To a solution of the product of the preceding reaction (40.74 g, 100 mmol) in acetone (150 mL) was added 4-methylmorpholine-N-oxide (60 wt% in H_2O, 19 mL, 110 mmol), H_2O (20 mL), and OsO_4 (255 mg, 1 mmol) in that order. The resultant dark purple solution was stirred at room temperature for 20h, then sodium hydrosulfite (3 g) was added and stirring was continued for 1h. The mixture was filtered and the acetone was removed by evaporation. The residue was diluted with H_2O (400 mL) and extracted with CH_2Cl_2 (3 X 200mL). The combined organic layers were washed with H_2O (2 X 200 mL) and brine (3 X 200 mL), dried ($MgSO_4$) and evaporated to give a dark brown syrup which was chromotographed (SiO_2, Et_2O: hexane

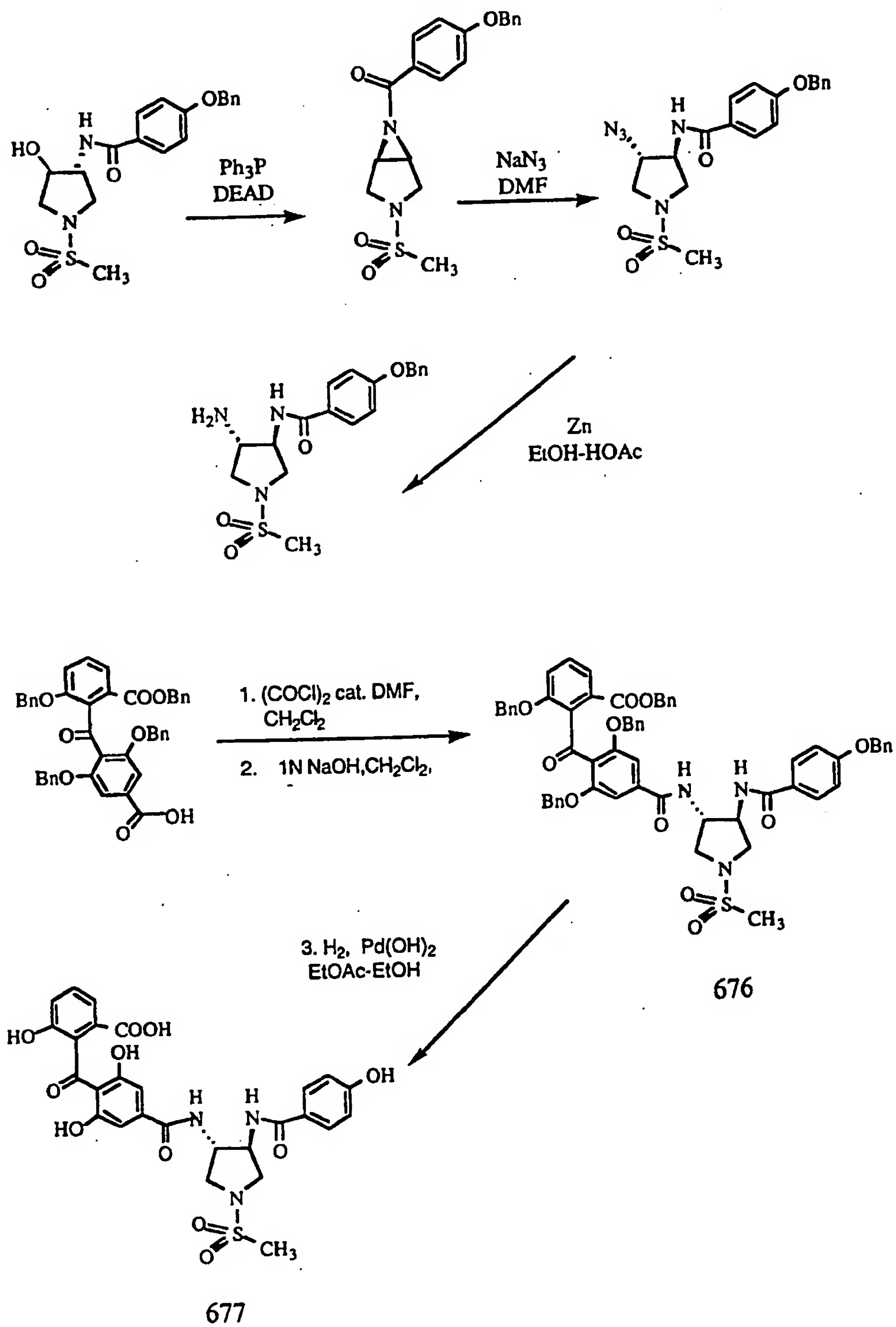
= 1 : 10 followed by Et_2O: hexane = 1 : 4) to give a colorless solid (35.2 g, 80%). A solution of $NaIO_4$ (68.23 g, 319 mmol) in H_2O (500 mL) was added dropwise over 5 min. to the product of the preceding reaction (35.20 g, 80 mmol) in THF (600 mL) at 5°C. The cooling bath was removed upon completion of addition and the mixture was stirred at room temperature for 1h. Et_2O (600 mL) was added and the mixture was washed with H_2O (3 X 300 mL) and brine (500 mL), dried ($MgSO_4$) and concentrated. The residue was dissolved in Et_2O (400 mL), diluted with MeOH (400 mL), cooled to 5°C, and then $NaBH_4$ (4.53 g, 119.63 mmol) was added portionwise. The resultant mixture was stirred at 5°C for 15 min. and then quenched by addition of H_2O (400 mL). The volatiles were evaporated leaving a thick syrup that was diluted with H_2O (400 mL) and extracted with CH_2Cl_2 (3 X 300 mL). The combined CH_2Cl_2 extracts were washed with H_2O (2 X 300 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2, Et_2O: hexane = 2 : 3) to give a colorless oil (8.25 g, 23%). MeLi in Et_2O (1.4 M, 18 mL, 25.26 mmol) was added dropwise to a solution of the product of the preceding reaction (5.6 g, 12.63 mmol) in THF (63 mL) at 5°C and the resultant solution was stirred at 5°C for 40 min. The cooling bath was removed and DMAP (154 mg, 1.26 mmol), followed by tosyl chlorine (4.46 g, 27.79 mmol), was added. The mixture was stirred at room temperature for 17h, poured into H_2O (100 mL), and extracted with CH_2Cl_2 (3 X 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed (SiO_2, Et_2O: hexane = 1 : 20 followed by Et_2O: hexane = 1 : 10) to give a colorless oil (2.32 g, 30%). A solution of the product of the previous reaction (2.06 g, 3.34 mmol) and 18-Crown-6 (1.765 g, 6.68 mmol) in DMSO (35 mL) was stirred and cooled with an ice-H_2O bath, and KO_2 (1.902 g, 26.75 mmol) was added in several portions. After 5 min. the cooling bath was removed and the mxiture was stirred at room temperature for 40 min. The resultant yellow solution was poured into H_2O (100 mL) and extracted with CH_2Cl_2 (3 X 30 mL). The combined CH_2Cl_2 extracts were washed with H_2O (2 X 30 mL)

and brine (2 X 30 mL), dried ($MgSO_4$), and evaporated to give a pale yellow oil (1.35 g, 83%) which was used in the next step without further purification.

n-BuLi in hexane (1.6 M, 1.83 mL, 2.92 mmol) was added dropwise over 10 min. to a solution of the oil from the reaction above (1.35 g, 2.92 mmol) in m-xylene (29 mL). The resultant solution was stirred at room temperature for 40 min. and then heated to reflux for 16h. The mixture was cooled to room temperature, diluted with Et_2O (10 mL), washed with H_2O (3 X 10 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2, Et_2O: hexane = 1 : 20) to give a colorless oil (550 g, 44%). A mixture of this product (500 mg, 1.17 mmol) and $Pd(OH)_2$ on carbon (20 wt%, contains ≤ 50% moist, 165 mg, 0.12 mmol) in MeOH (23 mL) was treated with H_2 (1 atm, balloon) at room temperature for 20 h. The mixture was filtered through Celite and the Celite pad was washed with more MeOH. The combined filtrates were evaporated to give a white solid (236 mg, 83%). A mixture of 4-benzyloxybenzoic acid (259 mg, 1.13 mmol) and 1,1'-carbonyldimidazole (183 mg, 1.13 mmol) in THF (3 mL) was stirred at room temperature for 2h, and then the above amine (230 mg, 0.94 mmol) in THF (3 mL) was added. Stirring was continued at room temperature for 24 h, and the resultant solution was diluted with EtOAc (15 mL), washed with H_2O (3 X 15 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2, Et_2O: hexane = 1 : 4) to give a white solid (276 mg, 65%). Tetrabutylammonium fluoride in THF (1 M, 0.62 mL, 0.62 mmol) was added to a stirred solution of the product of the previous reaction (270 mg, 0.59 mmol) in THF (1.8 mL). The mixture was stirred at room temperature for 2h, diluted with CH_2Cl_2 (10 mL), washed with H_2O (3 X 5 mL), dried ($MgSO_4$), and evaporated. The residue was dissolved in CH_2Cl_2 (10 mL), diluted with hexane (5 mL), and concentrated to about 5 mL at 0°C. The precipitate was collected and dried to give a white powder (122 mg, 61%). Oxalyl chloride in CH_2Cl_2 (2 M, 0.175 mL, 0.35 mmol) was added dropwise to a mixture of 4-(2-benzyloxy-6-(benzyloxycarbonyl)benzoyl)-3,5-dibenzyloxybenzoic

acid (160 mg, 0.23 mmol) and 1 drop of DMF in CH_2Cl_2 (1.2 mL) at 5°C. The mixture was stirred at room temperature for 2h and evaporated. The residue was dried *in vacuo* for 1 h, dissolved in CH_2Cl_2 (1.2 mL), and added to a mixture of the product of the previous reaction (60 mg, 0.18 mmol), Et_3N (0.049 mL, 0.35 mmol), and DMAP (ca. 2 mg, 0.018 mmol) in CH_2Cl_2 (0.9 mL) at 5°C. The cooling bath was removed and the mixture was stirred at room temperature for 18h. The resultant solution was diluted with CH_2Cl_2 (10 mL), washed with H_2O (3 X 5 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2, Et_2O: hexane = 1:1 followed by Et_2O: hexane: CH_2Cl_2 = 1:1:1) to give a colorless oil (143 mg, 80%) (Compound 635). A mixture of Compound 635 (118 mg, 0.12 mmol), $Pd(OH)_2$ on carbon (20 wt% contains ≤ 50% moist, 17 mg, 0.012 mmol), THF (1.2 mL), and MeOH (1.2 mL) was stirred vigorously under 1 atm H_2 contained in a balloon, at room temperature for 16 h. The resultant mixture was filtered through Florisol and the filtrate was evaporated to give a yellow solid (61 mg, 94%) (Compound 557). IR (KBr, cm^{-1}): 1702, 1679, 1649, 1641. FBMS: m/Z = 552 (M + 1).

(±)-*trans*-N-Methylsulfonyl-3-(4-hydroxybenzamido)-4-[3,5-dihydr xy-4-(2-carboxy-6-hydroxybenzoyl)benzamido]pyrrolidin (Comp und 677)

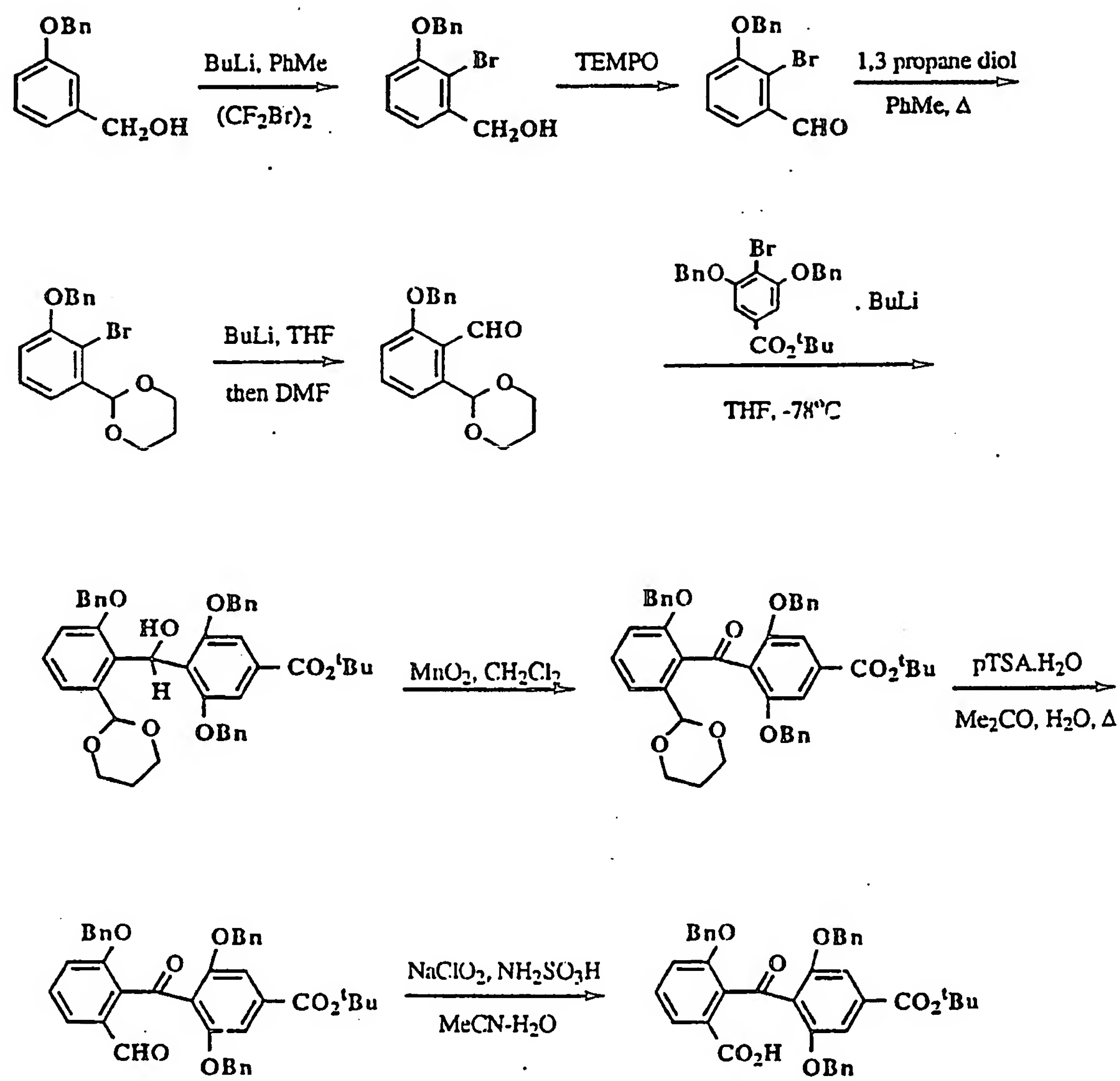


To a suspension of amidoalcohol (372 mg, 0.95 mmol) and Ph_3P (262 mg, 1.0 mmol) in anhydrous THF (10 mL) was added a solution of DEAD (174 mg, 158 μl, 1.0 mmol) in THF (2 mL) at 0°C. The mixture was allowed to stir at room temperature for overnight before an extractive workup. The crude product was purified by flash chromatography with 5 : 3 : 1/EtOAc: hexane: CH_2Cl_2 as an eluent to afford white solids. Recrystallization of the solids with MeOH three time yielded pure product (142 mg, 40%). The mixture of the aziridine from the previous reaction (142 mg, 0.38 mmol), NaN_3 (50 mg, 0.78 mmol) in anhydrous DMF (2.5 mL) was stirred at 50°C for 2h. Upon usual extractive workup, product was obtained as white solids (quant. yield) and used for the next step of reaction without further purification. To a suspension of the azido product of the preceding reaction (150 mg, 0.36 mmol) in 8 : 1 : 1 / EtOH: HOAc: H_2O (100 mL) was added Zn dust (118 mg, 1.80 mmol). After reaction at room temperature for 3h, the reaction mixture was worked up as usual and the crude product (140 mg) was used for the next step of reaction without purification. To a solution of benzophenone acid (305.4 mg, 0.45 mmol) in CH_2Cl_2 (5 mL) was added cat. DMF and oxalyl chloride (2.0 M solution in CH_2Cl_2, 0.56 mL, 1.13 mmol) at room temperature. The mixture was kept stirring at room temperature for 2 hr. Solvents were removed and the acid chloride residue was taken into CH_2Cl_2 (10 mL) after drying over the vacuum for 1 hr.

A biphasic mixture of the amino amide product of the previous reaction (140 mg, 0.36 mmol) in CH_2Cl_2 (10 mL) and 1N NaOH (4 mL) was treated with the freshly made acid chloride-CH_2Cl_2 solution (10 mL) at 5°C. The reaction mixture was allowed to stir at room temperature for 2h. The organic layer was separated and chromatographed on silica gel eluting with 2 : 1 / EtOAc: hexane to afford white solids (Compound 676) (150 mg, 40% from the amido-azide species). Compound 676 (140 mg, 0.133 mmol) was dissolved in EtOAc-HOEt (3 : 1, 20 mL) and treated with 10% $Pd(OH)_2$ (105 mg, 74 mol %). The mixture was subject to hydrogenolysis at 50 psi for 15hr. Solvents were concentrated after filtering through a pad of Celite, and the

residue was chromatographed eluting with 15% to 30% MeOH in EtOAc to yield yellow solids (50 mg, 63%) (Compound 677). The solids contained silica and failed to give silica free product after further HPLC purification. IR (KBr) cm^{-1} 3405, 1635, 1605, and 1547. Anal. Calcd. for $C_{27}H_{25}N_3O_{11}S$ • 1.5MeOH • 1.0H_2O • silica: C, 47.17; H, 4.58; N, 5.79, S, 4.42. Found: C, 47.22; H, 4.42; N, 5.68, S, 4.30. LRFAB (M + 1) : 600.

3-Benzyloxy-2-[2,6-dibenzyloxy-4-(t-butoxycarbonyl)benzoyl]benzoic acid



2-(2-Br mo-3-benzyloxyphenyl)-1,3-dioxane

The bromo alcohol (251 g, 0.86 mol) was dissolved in THF (300 ml) and sodium bromide (13.2 g, 0.128 mol) added. The reaction mixture was cooled to 0°C and TEMPO (0.67 g, 4.28 mmol) was added followed by a freshly prepared (0°C) solution of sodium bicarbonate (10.8 g, 0.128 mol) in 1 liter of commercial Chlorox bleach. This was stirred rapidly at 0°C for 3 h and sodium sulfite added. Any precipitated solids were dissolved upon addition of DI water. The organics were separated and the aqueous extracted with ethyl acetate. The combined organics were washed with brine, dried ($MgSO_4$) and concentrated. The residue was cooled in an ice bath and the precipitated solids collected by filtration to give the aldehyde (224 g, 90%): mp 125-6°C. Anal. Calcd. for $C_{14}H_{11}OBrO_2$, C, 57.76, H, 3.81. Found: C, 57.68, H, 3.77. The above prepared aldehyde (215 g) was combined in toluene (200 ml) with 1,3-propane diol (107 ml, 1.48 mol) and pTSA.H_2O (1.6 g) and heated at the reflux temperature with azeotropic removal of water *via* a Dean-Stark trap. After 1.5 h the reaction mixture was cooled and washed with saturated sodium bicarbonate and brine. The organics were separated, dried ($MgSO_4$) and evaporated. The residue was crystallized from methanol to afford product as a white solid (248 g, 96%): mp 73-4°C. Anal. Calcd. for $C_{17}H_{17}O_3Br$ C, 58.47, H, 4.91. Found: C, 58.52, H, 4.76.

2-(2-Formyl-3-benzyloxyphenyl)-1,3-dioxane

n-BuLi (236.2 ml of a 1.6 M solution in hexanes, 0.378 mol) was added dropwise to a solution of the product of the preceding reaction (120 g, 0.344 mol) in dry THF (600 ml) at -78°C. The temperature was maintained <-60°C during this time and stirring was continued for an additional 15 minutes after the final addition. Anhydrous DMF (532.2 ml, 6.87 mol) was then added dropwise whilst maintaining temperature <-60°C. The resulting solution was stirred at -60°C for 4hr and allowed to slowly warm to ambient temperature and allowed to stir overnight (16hr). The reaction was quenched upon addition of

saturated ammonium chloride solution and the solvents (THF, DMF) were removed *in vacuo*. The residue was partitioned between ethyl acetate and brine. The organics were sequentially washed with brine and water several times, dried ($MgSO_4$) and evaporated to a solid which was recrystallized from ethyl acetate-hexanes to give the product (80.7 g, 79%): mp 85-7°C. Anal. Calcd. for $C_{18}H_{18}O_4$ C 72.47, H, 6.08. Found: C, 72.26, H, 5.86.

1,1,-Dimethylethyl-4-[2-benzyloxy-6-(1,6-dioxanyl)phenylhydroxymethyl]-3,5-dibenzyloxybenzoate

n-BuLi (77.86 ml of 2.5 M solution in hexanes, 0.195 mol) was added dropwise to a -70°C solution of the aryl bromide (83.1 g, 0.177 mol) in anhydrous THF (800 ml) at a rate to maintain the internal temperature <-65°C. After the final addition the mixture was stirred for a further 10 min., whereupon the purple colored solution was added quickly *via* cannula to a -70°C solution of the THP-aldehyde (44.0 g, 0.147 mol) in dry THF (800 ml). The resulting yellow reaction mixture was stirred at this temperature overnight at which time solid ammonium chloride was added and was then allowed to warm to ambient temperature. DI (700 ml) water was then added and the organic layer was separated. The aqueous was extracted with ethyl acetate and the combined organics were washed with brine, dried ($MgSO_4$) and evaporated to afford a yellow oil which was chromatographed (SiO_2, 15% ethyl acetate-hexanes). The product was isolated as a white foam (62.23 g, 61%). Anal. Calcd. for $C_{43}N_{44}O_8$ C, 74.98, H, 6.44. Found: C, 74.76, H, 6.24.

1,1,-Dimethylethyl 4-[2-benzyloxy-6-(1,6-dioxanyl)benzoyl]-3,5-dibenzyloxybenzoate

Manganese dioxide (250 g) was added in portions to a stirred solution of the product of the preceding reaction (62.2 g, 0.090 mol) in methylene chloride (1.5 L). The reaction mixture was allowed to stir overnight at ambient temperature and the MnO_2 was removed by filtration through celite. The pad was washed with further methyl ne chloride and the filtrates

were evaporated to afford the ketone product as a white foam (59.81 g, 96%). Anal. Calcd. for $C_{43}H_{42}O_8$ C, 75.20, H, 6.16. Found: C, 75.17, H, 6.04.

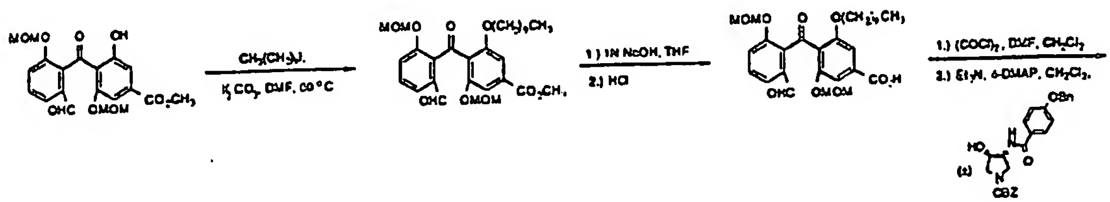
1,1,-Dimethylethyl 3,5-Dibenzyloxy-4-[6-benzyloxy-2-formylbenzoyl]benzoate

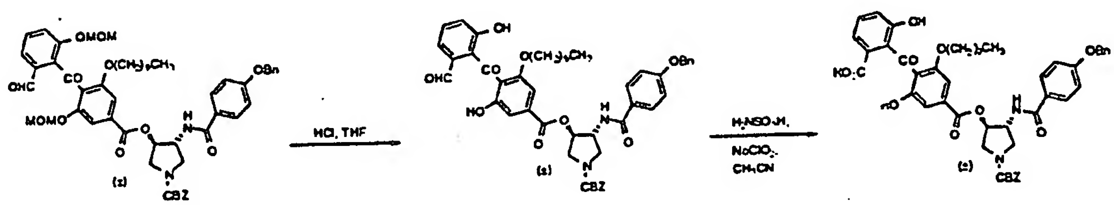
The ketone product from the preceding reaction (58.0 g, 0.084 mol) was dissolved in acetone (270 ml) and DI water (30 ml). A catalytic amount of pTSA•H_2O was added and the mixture refluxed for 3 hrs. Saturated sodium bicarbonate solution was added to adjust the pH to a basic level and the acetone was removed *in vacuo*. The aqueous was extracted with ethyl acetate and the organics dried ($MgSO_4$) and evaporated. The residue was crystallized from methanol to afford the aldehyde product (50.48 g, 95%) as a light yellow solid which was identical with material prepared by the original route.

3-Benzyloxy-2-[2,6-dibenzyloxy-4-(1,1-dimethylethoxycarbonyl)benzoyl]benzoic acid

A solution of sulfamic acid (4.01 g, 0.041 mol) in DI water (50 ml) was added to a solution of the aldehyde product of the previous reaction (20.0 g, 0.0318 mol) in acetonitrile (300 ml) at ambient temperature. After 5 minutes a solution of sodium chlorite (4.82 g, of 80%, 0.043 mol) in DI water (50 ml) was added dropwise. Once complete the reaction mixture was stirred for 30 minutes. The solvent was removed *in vacuo* and the aqueous was extracted several times with ethyl acetate. The organics were combined, dried ($MgSO_4$) and evaporated to afford the acid product (20.9 g) which was identical with material prepared by the original route.

(±)-Trans-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-hydroxycarbonylbenzoyl)-3-decyloxy-5-hydroxybenzoyloxy]pyrrolidinium trifluoroac tate (Compound 755)





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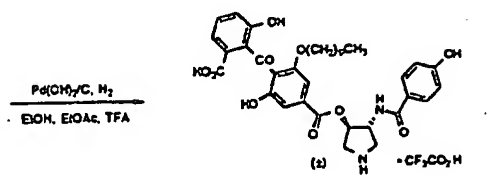

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Methyl 4-(2-methoxymethyleneoxy-6-formylbenzoyl)-3-decyloxy-5-methoxymethyleneoxybenzoate

Iododecane (174 μL, 0.816 mmol) was added to a stirred mixture of Methyl 4-(2-methoxymethyleneoxy-6-formylbenzoyl)-3-hydroxy-5-methoxymethyleneoxybenzoate (0.300 g, 0.742 mmol) and K_2CO_3 (0.113 g, 0.816 mmol) in N,N-DMF (7 mL) at room temperature under a nitrogen atmosphere. The mixture was heated to 60°C for 3h. The solvent was evaporated *in vacuo* and the residue partitioned between EtOAc (75mL) and water (50mL). The organic phase was separated and washed with water (50mL)

and brine (50 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Subsequent chromatography of the oily residue on silica gel eluting with 30% EtOAC/Hex afforded the title compound (0.328 g, 81%) as a colorless oil.

4-(2-methoxymethyleneoxy-6-formylbenzoyl)-3-decyloxy-5-methoxymethyleneoxybenzoic acid

1N NaOH (8mL) was added to a solution of Methyl-4-(2-methoxymethyleneoxy-6-formylbenzoyl)-3-decyloxy-5-methoxymethyleneoxybenzoate (0.300 g, 0.551 mmol) in THF (8 mL). The mixture was stirred for 20h and was then acidified to pH 3 with 6N HCl. The THF was evaporated and the aqueous mixture extracted with EtOAc (150 mL). The organic phase was separated and washed with water (75mL) and brine (75mL) then dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound (0.248 g 85%) as an off white solid.

(±)-Trans-3-(4-benzyloxybenzamido)-4-[4-(2-methoxymethyleneoxy-6-formylbenzoyl)-3-decyloxy-5-methoxymethyleneoxybenzoyloxy]-N-benzyloxycarbonylpyrrolidine (Compound 752)

Oxalyl chloride (234 μL, 2.0 M) in CH_2Cl_2 added to a stirred solution of 4-(2-methoxymethyleneoxy-6-formylbenzoyl)-3-decyloxy-5-methoxymethyleneoxybenzoic acid (0.248 g, 0.467 mmol) and N,N-DMF (50 μL) in CH_2Cl_2 (5mL) at 0°C under a nitrogen atmosphere. The solution was stirred at 0°C for 2h. The solvent was then evaporated *in vacuo* and the resulting residue dried under vacuum for 1.5h. A solution of the residue in CH_2Cl_2 (5 mL) was added dropwise to a stirred mixture of 4-benzyloxybenzamido-3-hydroxy-N-benzyloxycarbonylpyrrolidine (0.209 g, 0.467 mmol), Et_2N (195 μL, 1.4 mmol), and DMAP (0.069 g, 0.561 mmol) in CH_2Cl_2 (5mL) at 0°C under a nitrogen atmosphere. The mixture became homogenous as it was warmed to room temperature gradually and stirred for 16h. The solvent was evaporated and the residue chromatographed on silica gel eluting with 2% $MeOH/CH_2Cl_2$ to afford the title compound (0.234 g, 52%) as a yellow oil.

(±)-Trans-3-(4-benzyloxybenzamido)-4-[4-(2-hydroxy-6-formylbenzoyl)-3-decyl xy-5-hydroxybenz yloxy]-N-benzyloxycarbonylpyrrolidine (Compound 753)

Concentrated aqueous HCl (65 µL) was added to a stirred solution of (±)-trans-3-(4-benzyloxybenzamido)-4-[4-(2-methoxymethyloxy-6-formylbenzoyl)-3-decyloxy-5-methoxymethyloxybenzoyloxy]-N-benzyloxycarbonylpyrrolidine (0.234 g, 0.244 mmol) in THF (2mL). The resulting mixture was stirred at room temperature for 16h. Concentrated aqueous HCl (65µL) was again added and the mixture stirred for 72h. The mixture was concentrated *in vacuo* and the residue partitioned between EtOAc (100 mL) and water (75mL). The organic portion was separated and washed with water (50mL) and brine (50mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Subsequent chromatography of the residue eluting with 2% $MeOH/CH_2Cl_2$ afforded compound 753 as a yellow oil.

(±)-Trans-3-(4-benzyloxybenzamido)-4-[4-(2-hydroxy-6-hydroxycarbonylbenzoyl)-3-decyloxy-5-hydroxybenzoyloxy]-N-benzyloxycarbonylpyrrolidine (Compound 754)

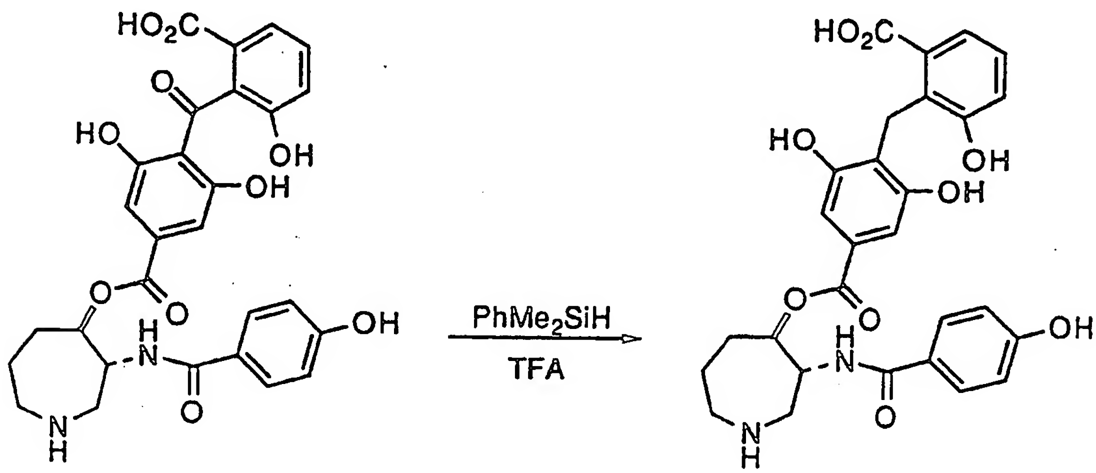
A solution of sulfamic acid (9.7 mg, 0.100 mmol) in water (0.5mL) was added to a stirred solution of Compound 753 (67 mg, 0.077 mmol) in CH_3CN (5mL) at room temperature. The resulting solution was stirred for 5 min then a solution of sodium chlorite (12 mg, 0.129 mmol, 80%) in H_2O (0.5mL) was added and the resulting solution stirred at room temperature for 1.5h. The solution was concentrated and the residue partitioned between EtOAc (50mL) and water (30 mL). The organic phase was separated and washed with water (20mL) and brine (20mL) then dried ($MgSO_4$) and concentrated *in vacuo* to afford compound 754 (25 mg, 35%) as a yellow oil.

(±)-Trans-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-hydroxycarbonylbenzoyl)-3-decyloxy-5-hydroxybenzoyloxy]pyrrolidinium trifluoroacetate (Compound 755)

Moist palladium hydroxide on carbon (12 mg, 20% Pd) was added to a stirr d solution of (±)-Trans-3-(4-benzyloxybenzamido)-4-[4-(2-hydroxy-6-hydroxycarbonylbenzoyl)-

3-decyloxy-5-hydroxybenzoyloxy]-N-benzyloxycarbonylpyrrolidine (24 mg, 0.027 mmol) in EtOH (2mL), EtOAc (2mL) and TFA (0.1mL). The mixture was stirred under 1 atm. of hydrogen for 16h. The mixture was filtered and the filtrate concentrated *in vacuo*. Moist palladium hydroxide on carbon (20 mg, 20W% Pd) was added to a solution of the residue in EtOH (3mL) and TFA (0.5mL) and the mixture was stirred under 1 atm. of hydrogen again for 16h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was chromatographed on a 21X250 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0-100% B over 60m; flow: 15 mL/min) affording compound 755 as a pale yellow foam.

(±)-Trans-4-[4-(2-carboxy-6-hydroxybenzyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)perhydroazepine Trifluoroacetate Salt Hydrat (Compound 756)



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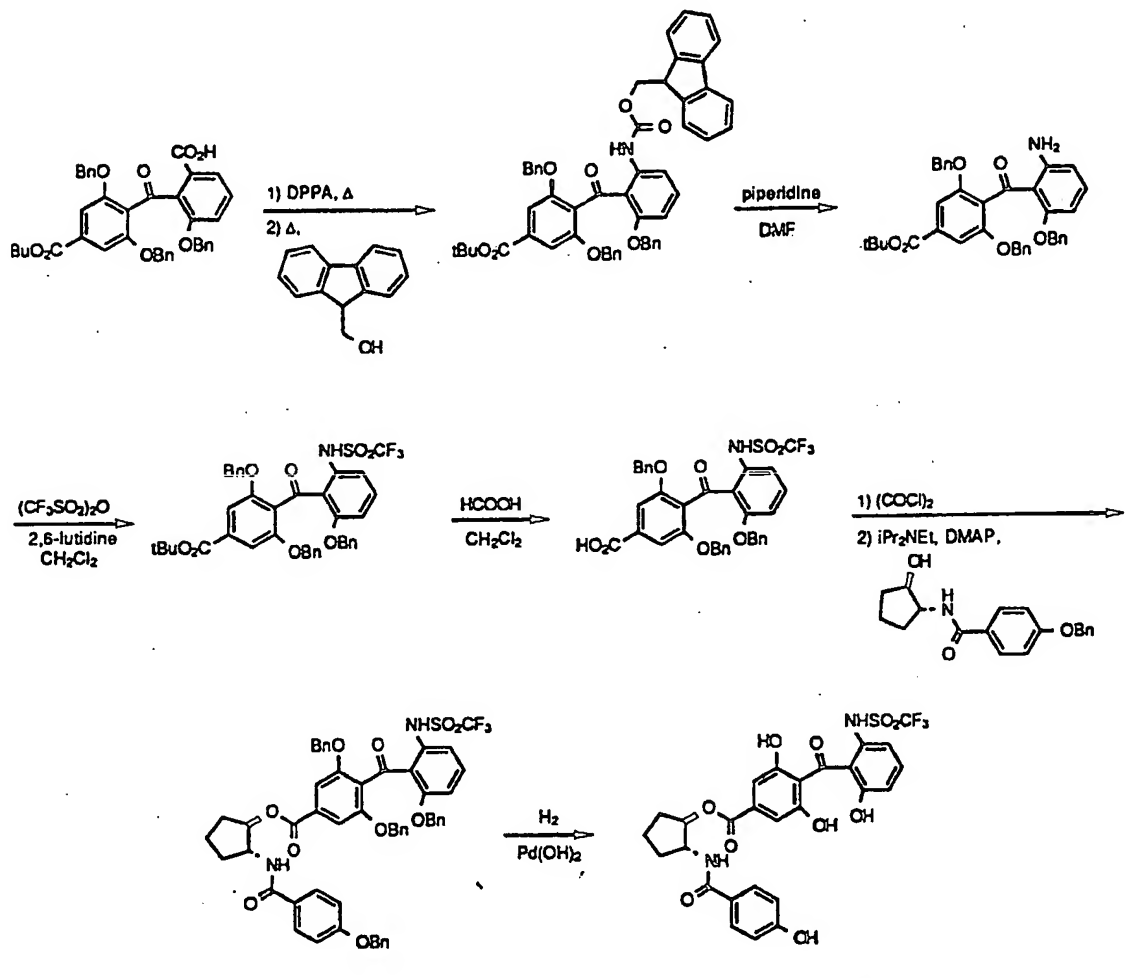
A solution of 70 mg (0.097 mmol) of trans-4-(4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy)-3-(4-hydroxybenzamido)perhydroazepine trifluoroacetic acid salt hydrate in 5mL of trifluoroacetic acid was treated with a total of 428 μL (2.79 mmol) of phenyldimethylsilane in four portions over a period of 26 days, during which time the reaction mixture was stirred at room temperature. The mixture was evaporated to a residue which was chromatographed on a 21 X 250 mm C18 column (solvent A:95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0-50% B over 60 min, flow: 15 mL/min). The fractions which contained the desired product were pooled and lyophilized to give 6.0 mg of partially purified material, which was rechromatographed as stated above, using this time a 0-25% B over 60 min gradient. The pure

fractions were pooled and evaporated and then lyophilized from water to give 1.0 mg of the title compound as a tan fluffy solid. FABMS: m/z 537 (M+H); HRMS: calcd for $C_{28}H_{29}N_2O_9$: 537.1873, found 537.1866.

(±)-Trans-2-[3,5-Dihydroxy-4-(2-hydroxy-6-(trifluoromethane-sulfonylamino)benzoyl)benzoyloxy]-1-(4-hydr xybenzamido)-cyclopentane Hemihydrate (Compound 758)



757 758

4-[6-Benzyloxy-2-[[(9-fluorenylmethoxy)carbonyl]amino]benzoyl]-3,5-dibenzyloxybenzoic Acid 1,1-Dimethylethyl Ester

A suspension of 1.02g (1.58 mmol) of 4-(6-benzyloxy-2-carboxybenzoyl)-3,5-dibenzyloxybenzoic acid 1, 1-dimethylethyl ester in 7 mL of toluene was treated with 221 µL (160 mg, 1.59 mmol) of triethylamine and 341 µL (435 mg, 1.58 mmol) of diphenylphosphoryl azide, and the mixture was heated at 90°C under a nitrogen atmosphere for 1h. To this mixture was added 621 mg (3.16 mmol) of 9-fluorenemethanol, and the mixture was stirred at 90°C under a nitrogen atmosphere for 16h. The mixture was cooled, diluted with 100 mL of ether, washed twice with half-saturated sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated to give 1.75 g of the crude product. Chromatography on silica gel eluting with 80/20/3 hexane - toluene - isopropanol gave 1.53 g of the crude title compound as a yellow oil, which was used directly in the next step.

4-(2-Amino-6-benzyloxybenzoyl)-3,5-dibenzyloxybenzoic Acid 1,1-Dimethylethyl Ester

A solution of 1.53 g (1.8 mmol) of crude 4-[6-benzyloxy-2-[[(9-fluorenylmethoxy)carbonyl]amino]benzoyl]-3,5-dibenzyloxy acid 1,1-dimethylethyl ester in 20 mL of 9/1 DMF - piperidine was stirred at room temperature under a nitrogen atmosphere for 6h. The mixture was diluted with 400 mL of ether, washed with 5% citric acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated to give 1.30 g of the crude product, which was used directly in the next step.

4-[2-Benzyloxy-6-(trifluoromethylsulfonylamino)benzoyl]-3,5-dibenzyloxybenzoic Acid 1,1-Dimethylethyl Ester

A solution of 1.30 g (1.8 mmol) of crude 4-(2-amino-6-benzyloxybenzoyl-3,5-dibenzyloxybenzoic acid 1,1-dimethylethyl ester in 30 mL of methylene chloride was treated at 0°C with 0.56 mL (0.52 g, 4.8 mmol) of 2,6-lutidine and 0.639 mL (1.07 g, 3.8 mmol) of triflic anhydride, and the mixture was stirred at 0-10°C under a nitrogen atmosphere for 3.5h. An additional

0.18 mL of 2,6-lutidine and 0.21 mL of triflic anhydride was then added, and the mixture was stirred for an additional 2h. The mixture was diluted with 300 mL of ether, washed twice with 5% citric acid and once with brine, dried over magnesium sulfate, and evaporated to give 1.77 g of the crude product. Chromatography on silica gel eluting with 4/1 hexane - ethyl acetate gave 0.38 g (32% over three steps based on starting carboxylic acid) of the title compound as a yellow oil, which was used directly in the next step.

4-[2-Benzyloxy-6-(trifluoromethylsulfonylamino)benzoyl-1-3.5-dibenzyloxybenzoic Acid

A solution of 0.38 g (0.51 mmol) of 4-[2-benzyloxy-6-(trifluoromethylsulfonylamino)benzoyl-3,5-dibenzyloxybenzoic acid 1,1-dimethylethyl ester in 5 mL of methylene chloride was treated with 10 mL of formic acid, and the mixture was stirred at room temperature for 8 h. The mixture was evaporated to give 0.35 g crude residue, which was purified by chromatography of a 41 x 300 mm C18 column (solvent A 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 25-100% B over 60 min, flow: 25 mL/min). The pure fractions were combined, evaporated and then lyophilized from water to give 179 mg (51%) of the title compound as a white solid, which was taken directly to the next step.

(±)-trans-2-[4-[2-Benzyloxy-6-(trifluoromethylsulfonylamino)-benzoyl]-3,5-dibenzyloxybenzoyloxy]-1-(4-benzyloxybenzamido)cyclopentane (Compound 757)

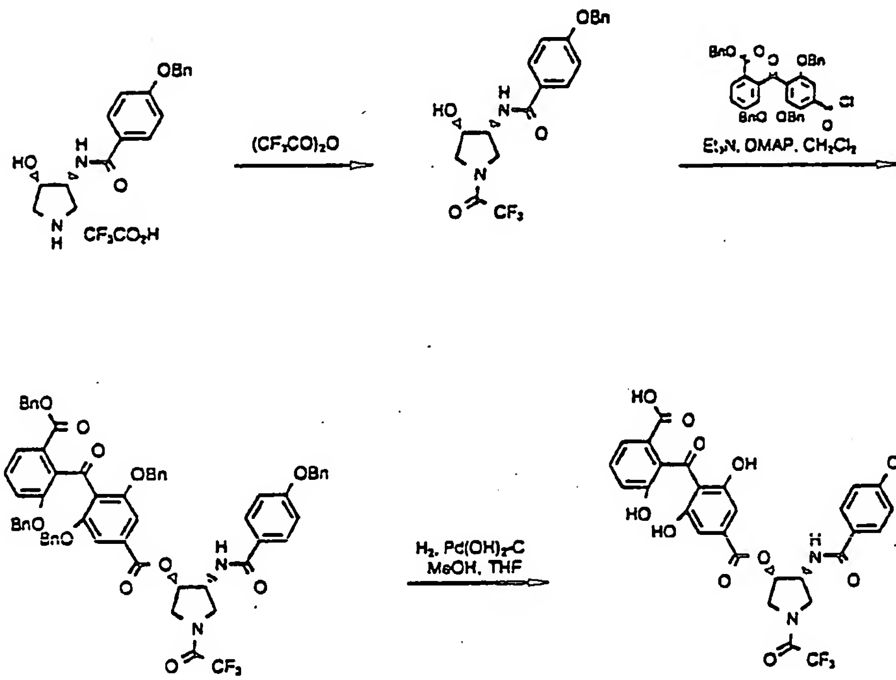
A suspension of 178 mg (0.257 mmol) of 4-[2-benzyloxy-6-(trifluoromethylsulfonylamino)benzoyl]-3,5-dibenzyloxybenzoic acid in 5 mL of methylene chloride containing a trace (approximately 1 μL) of dimethylformamide was cooled to 0°C. Oxalyl chloride (200 μL, 0.40 mmol) was added, and the mixture was stirred under a nitrogen atmosphere for 3 h, after which time the solution had become homogeneous. The reaction mixture was evaporated, and the residue was evaporated twice from 20 mL of methylene chloride. The residue was dissolved in 8 mL of

methylene chloride, and 88.2 mg (0.283 mmol) of trans-1-(4-benzyloxybenzamido)-2-hydroxycyclopentane, 53.8 μl (0.309 mmol) of diisopropylethylamine, and 3 mg of DMAP were added. The mixture was stirred at room temperature under a nitrogen atmosphere for 17 h, after which it was diluted with 300 mL of methylene chloride, washed with 2 N HCl and brine, dried over magnesium sulfate, and evaporated to give 310 mg of the crude product. Chromatography on silica gel eluting with 97/3 methylene chloride - ethyl acetate gave 36.5 mg (14%) of the title compound as a yellow oil, which was used directly in the next step.

(±)-Trans-2-[3,5-Dihydroxy-4-(2-hydroxy-6-(trifluoromethanesulfonylamino)benzoyl)benzoyloxy]-1-(4-hydroxybenzamido)-cyclopentane Hemihydrate (Compound 758)

A solution of 36 mg (0.037 mmol) of (±)-trans-2-[4-[2-benzyloxy-6-(trifluoromethylsulfonylamino)benzoyl]-3,5-dibenzyloxybenzoyloxy]-1-(4-benzyloxybenzamido)cyclopentanein 6 mL of 1/1 ethanol - ethyl acetate was treated with 6.4μL of trifluoroacetic acid. Moist 10% palladium hydroxide on carbon (16.0 mg) was added, and the mixture was stirred under an atmosphere of hydrogen for 7 h. The mixture was filtered, evaporated, and the residue was chromatographed on a 21 x 250 mm C18 column (solvent A: 9:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0-50% B over 60 min, flow: 15 mL/min). The pure fraction was evaporated and then lyophilized from water to give 11.8 mg (51%) of the title compound as a yellow fluffy solid. IR (KBr) : 1705, 1633, 1611, 1506, 1428, 1370, 1229, 1201, 1141, 1031 cm^{-1}; FABMS: *m/z* 625 (M+H). Anal. Calcd for $C_{27}H_{23}F_3N_2O_{10}S \cdot 0.5\ H_2O$:C, 51.19 H, 3.82; N, 4.42; S, 5.06. Found C, 50.96; H, 3.76; N, 4.29; S, 4.91.

1-Trifluoroac tyl-trans-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-carboxybenzoyl)-3,5-dihydroxybenzoyloxyl]pyrrolidin (COMPOUND 560)



637 560

A solution of the shown pyrrolidinyl alcohol (213 mg, 0.5 mmol, see Compound 558 for preparation) in trifluoroacetic anhydride (2.5 mL) was stirred at room temperature for 2.5 h and then evaporated. The residue was dissolved in MeOH and stirred with 1 N aq. NaOH (0.5 mL) for 30 min. The white precipitate was collected by filtration, washed with H_2O (2 mL), dissolved in acetone (10 mL), dried ($MgSO_4$), and evaporated to give a white solid (173 mg, 85%).

COMPOUND 637

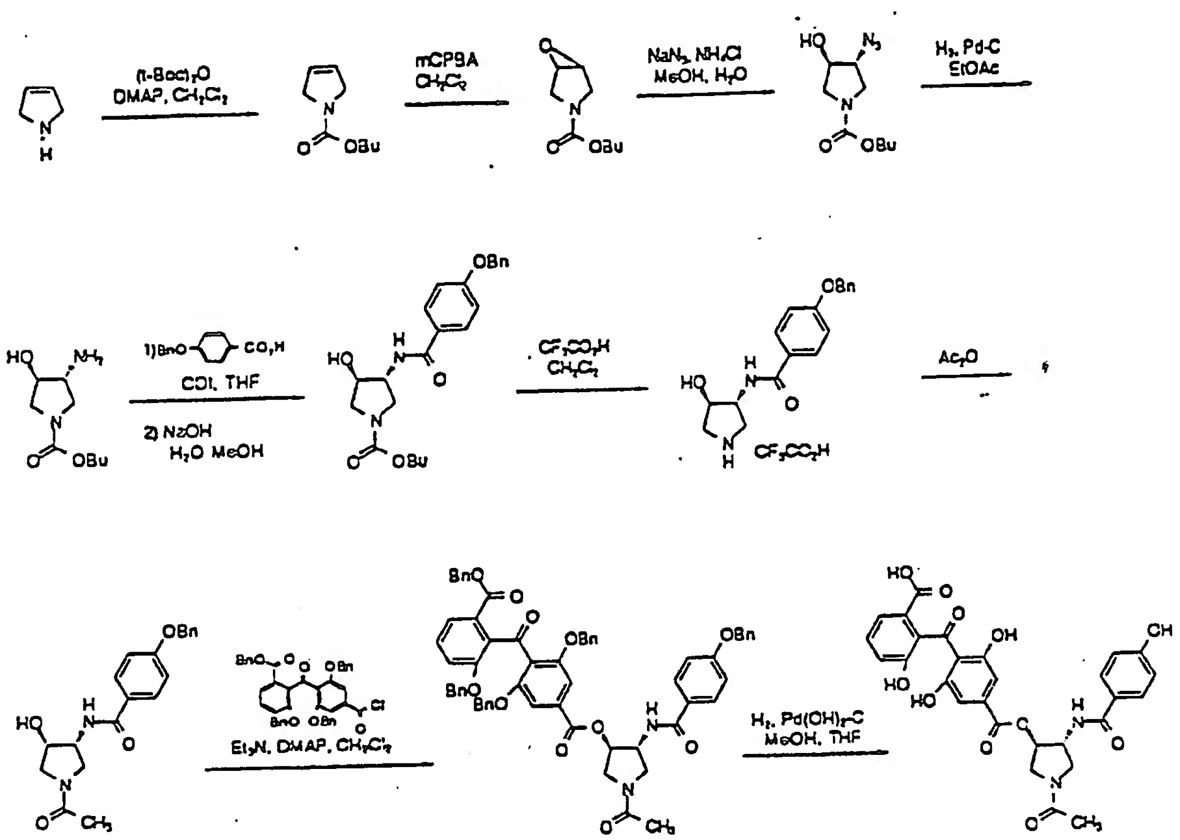
Oxalyl chloride in CH_2Cl_2 (2 M, 0.21 mL, 0.42 mmol) was added dropwise to a solution of 4-(2-benzyloxy-6-benzyloxycarbonylbenzoyl)-3,5-dibenzyloxybenzoic acid (190 mg,

0.28 mmol) and a drop of DMF in CH_2Cl_2 (1 mL) at 5°C. The mixture was stirred at room temperature for 2 h, then evaporated to remove the solvent and excess oxalyl chloride. The residue was dried *in vacuo* for 1 h, dissolved in CH_2Cl_2 (1mL), and added to a mixture of the product from the previous reaction (114 mg, 0.28 mmol), Et_3N (0.078 mL, 0.56 mmol), and DMAP (3 mg, 0.028 mmol) in CH_2Cl_2 (2 mL) at 5°C. The mixture was stirred at room temperature for 17 h, diluted with CH_2Cl_2 (10 mL), washed with H_2O (3 x 10 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2, EtOAc: hexane = 1:1) to give a pale yellow oil (169 mg, 56%), together with recovered product of the previous reaction (44 mg, 38%).

COMPOUND 560

$Pd(OH)_2$ on carbon (20 wt%, contains≤50% moist, 20 mg, 0.014 mmol) and MeOH (1.4 mL) was added to a solution of the product of the previous reaction (148 mg, 0.14 mmol) in THF (1.4 mL) and the mixture was stirred under 1 atm H_2 contained in a balloon at room temperature for 16 h. The mixture was filtered through Celite and the filtrate was evaporated to give a yellow solid that was purified by prep. TLC (SiO_2, EtOAc, product was washed off the silica gel with 1% AcOH in EtOaAc) to give a yellow solid (51 mg, 59%). IR (KBr, cm^{-1}): 1688, 1635, 1607. FBMS: M/Z = 619 (M+1).

1-Acetyl-trans-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-hydroxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxyl]pyrrolidine (COMPOUND 558)



636 558

To a solution of pyrrolidine (contains ca. 25% pyrrolidine, 10 mL, ca. 132 mmol) and DMAP (806 mg, 6.6 mmol) in CH_2Cl_2 (400 mL) at 5°C was added (^{t}Boc)$_2$O in small portions. After completion of addition the cooling bath was removed and stirring was continued for 2 h. The mixture was washed with H_2O (3 x 150 mL), dried ($MgSO_4$), and evaporated to give a pale yellow oil (22.86 g, 102%) which was shown by ^{1}H NMR to be the expected products contaminated by ^{t}BuOH. This material was used in the next step without further purification.

To a solution of the previous reaction product (16.93 g, ca. 70 mmol in N-Boc-pyrroline) in CH_2Cl_2 (140 mL) at 5°C was added mCPBA (80%, 17.81 g, 82.5 mmol) in several portions over 20 min. The mixture was stirred at 5°C for 30 min and then at room temperature for 24 h. The white precipitate was removed by filtration, the filtrate was washed successively with sat. aq. Na_2SO_3 (3 x 30 mL), sat. aq. $NaHCO_3$ (3 x 50 mL), and H_2O (2 x 50 mL), dried ($MgSO_4$), and evaporated to give a yellow oil which was chromatographed (SiO_2, Et_2O: hexane = 1:10 followed by Et_2O:hexane = 1.1) to give a product (6.67 g, 51%) and unreacted N-Boc-pyrroline (2.54 g, 22%).

A mixture of the previous reaction product (6.67 g, 36 mmol), NaN_3 (4.68 g, 72 mmol), NH_4Cl (1.93 g, 36 mmol), MeOH (72 mL), and H_2O (12 mL) was stirred for 15 h and then concentrated. The residue was treated with 1 N NaOH (50 mL) and extracted with CH_2Cl_2 (3 x 30 mL) (should use Et_2O instead of CH_2Cl_2 for the extraction to avoid possibility of detonation). The combined CH_2Cl_2 extracts were washed with H_2O (3 x 30 mL) and brine (2 x 30 mL), dried ($MgSO_4$), and evaporated to give a yellow oil (7.22 g, 88%).

A mixture of the previous reaction product (7.01 g, 30.72 mmol) and Pd on carbon (5%, 1.63 g, 0.77 mmol) in EtOAc (150 mL) was stirred vigorously under 1 atm H_2 contained in a balloon at room temperature for 20 h. The reaction was judged incomplete by TLC. More 5% Pd on carbon (1.36 g) was added and the reaction was allowed to continue for another 20 h. The mixture was diluted with MeOH (40 mL) and filtered through Celite. The filtrate was evaporated to give a yellow oil (3.897 g, 63%).

A mixture of 4-benzyloxybenzoic acid (5.03 g, 22.02 mmol) and 1, 1'-carbonyldiimidazole (3.57 g, 22.02 mmol) in THF (66 mL) was stirred at room temperature for 1.5 h and the previous reaction product (3.71 g, 18.35 mmol) in THF (9 mL) was added. The resultant mixture was stirred at room temperature for 4 h, washed with H_2O (3 x 50 mL), dried ($MgSO_4$), and evaporated. The residue was dissolved in MeOH (20 mL) and

THF (10 mL) and stirred with 1 N NaOH (20 mL) for 5h. The resultant white precipitate was collected by filtration, washed with H_2O (15 mL) and Et_2O (30 mL), and dried *in vacuo* to give a white solid that was recrystallized from hot THF once to give a fine white powder (5.22 g, 69%).

To a slurry of the previous reaction product (850 mg, 2.06 mmol) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (1.6 mL, 20.6 mmol) dropwise. The resultant solution was stirred at room temperature for 2 h and then poured into stirred Et_2O (100 mL). The precipitate was collected, washed with Et_2O, and dried *in vacuo* to give a white powder (579 mg, 66%).

Acetic anhydride (1.2 mL) was added to the previous reaction product (128 mg, 0.3 mmol) and the mixture was stirred at room temperature to result in a complete dissolution in ca. 10 min. After an additional 2.5 h a white precipitate was formed which was collected by filtration, washed with Et_2O (20mL), and dried *in vacuo* to give a white powder (67 mg, 63%).

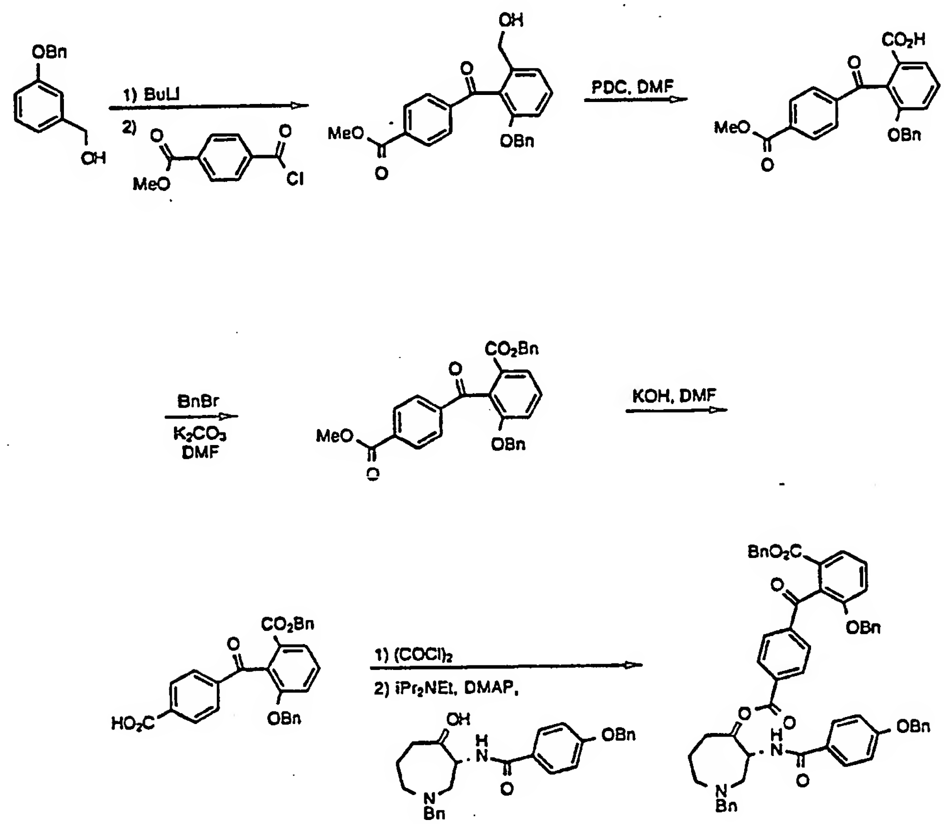
COMPOUND 636

Oxalyl chloride in CH_2Cl_2 (2 M, 0.19 mL, 0.38 mmol) was added to a mixture of 4-(2-benzyloxy-6-benzyloxycarbonylbenzoyl)-3,5-debenzyloxybenzoic acid (170 mg, 0.25 mmol) and a drop a DMF in CH_2Cl_2 (1 mL) at 5°C. The mixture was allowed to stir at room temperature for 2 h, and then evaporated to remove the solvent and excess oxalyl chloride. The residue was dried *in vacuo* for 1 h, dissolved in CH_2Cl_2 (1 mL) and added to a mixture of the previous reaction product (67 mg, 0.19 mmol), Et_3N (0.05 mL, 0.35 mmol), and DMAP (ca. 2mg, 0.019 mmol). The mixture was stirred at room temperature for 16 h, diluted with CH_2Cl_2 (15 mL), washed with H_2O (3 x 10mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2, EtOAc) to give a pale yellow oil (131 mg, 52%).

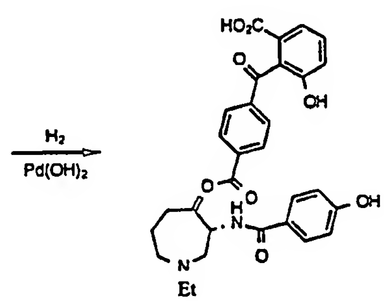
COMPOUND 558

$Pd(OH)_2$ on carbon (20 wt%, contains ≤50% moist, 18 mg, 0.013 mmol) and MeOH (1.3 mL) were added to a solution of Compound 636 (131 mg, 0.13 mmol) in THF (1.3 mL) and the mixture was stirred under 1 atm H_2 contained in a balloon at room temperature for 18 h. The mixture was filtered through Celite and evaporated to give a yellow solid (43 mg, 59%). IR (KBr, cm^{-1}): 1716, 1633, 1606. FABMS: M/Z = 565 (M+1).

Trans-N-Ethyl-4-(4-(2-carboxy-6-hydroxybenzoyl)benzoyloxy)-3-(4- hydroxybenzamido)azepine Trifluoroacetic Acid Salt Hydrate (COMPOUND 559)



634



559

Methyl-4-(6-Benzyloxy-2-hydroxym thylbenzoyl)benzoate

To a solution of 1.07 g (5.00 mmol) of 3-benzyloxybenzyl alcohol in 15 mL of toluene at -5 °C under an atmosphere of nitrogen was added 5.8 mL (12.2 mmol) of a 2.1 M solution of butyllithium in hexanes over 15 min. The solution was stirred at -5 °C for 6 h, after which it was cooled to -78 °C, and a solution of 1.00 g (5.03 mmol) of 4-(methoxycarbonyl)-benzoyl chloride in 5 mL of tetrahydrofuran was added. The mixture was stirred for 1 h, after which it was poured onto 200 mL of ether and 100 mL of saturated aqueous ammonium chloride, and this mixture was stirred for 10 min. The layers were separated, and the organic phase was washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated to give the crude product. Flash chromatography on silica gel eluting with 3/1 ethyl acetate - hexane afforded 0.68 g (36%) of the title compound as a white solid, which was carried on to the next step.

Methyl-4-(6-Benzyloxy-2-carboxybenzoyl)benzoate

To a solution of 0.63 g (1.7 mmol) of methyl 4-(6-benzyloxy-2-hydroxymethylbenzoyl)benzoate in 20 mL of dimethylformamide was added 4.41 g (11.7 mmol) of pyridinium dichromate. The solution was stirred at room temperature under a nitrogen atmosphere for 4 days, after which it was poured onto 300 mL of ether and washed with 200 mL of water, 150 mL of 2 M HCl, and 150 mL of brine, and dried over magnesium sulfate. Evaporation of the solvent afforded 0.47 g (72%) of the crude product. This material was sufficiently pure for further use and was carried directly to the next step.

Methyl-4-(6-Benzyloxy-2-(benzyloxycarbonyl)benzoyl)benzoate

To a solution of 0.47 g (1.2 mmol) of methyl 4-(6-benzyloxy-2-carboxybenzoyl)benzoate in 20 mL of dry dimethylformamide was added 501 mg (3.62 mmol) of potassium carbonate and 0.158 mL (227 mg, 1.32 mmol) of benzyl bromide.

The solution was stirred at room temperature under a nitrogen atmosphere for 18 h. The mixture was then poured onto 300 mL of ether and washed with two 200 mL portions of water and then with 150 mL of brine, and dried over magnesium sulfate. Evaporation of the solvent afforded 0.57 g of the crude product, which was chromatographed on silica gel, eluting with 3/1 hexane - ethyl acetate to give 0.32 g (54%) of the title compound as a colorless oil. This material was used directly in the next step.

4-(6-Benzyloxy-2-(benzyloxycarbonyl)benzoyl)benzoic acid

A solution of 0.301 g (0.614 mmol) of methyl 4-(6-benzyloxy-2-(benzyloxycarbonyl)benzoyl)benzoate in 7 mL of DMF was treated with 0.337 mL of a 2 M aqueous solution of potassium hydroxide under an atmosphere of nitrogen for 20 h. The mixture was then poured onto 100 mL of ethyl acetate and washed with 60 mL each of 0.2 N HCl, water,and brine. The organic extracts were dried over magnesium sulfate and evaporated to give 0.32 g of the crude product, which was chromatographed on a 41 x 250 mm C18 column (solvent A: 95:5 water/acetonitrile 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0-100% B over 60 min, flow: 25 mL/min). The pure fractions were pooled and evaporated and then lyophilized from water to give 70 mg of the title compound as a white solid, which was carried on as is to the next step.

Trans-N-Benzyl-4-(4-(6-benzyloxy-2-(benzyloxycarbonyl) benzoyl)benzoyloxy)-3-(4-benzyloxybenzamido)azepine (COMPOUND 634)

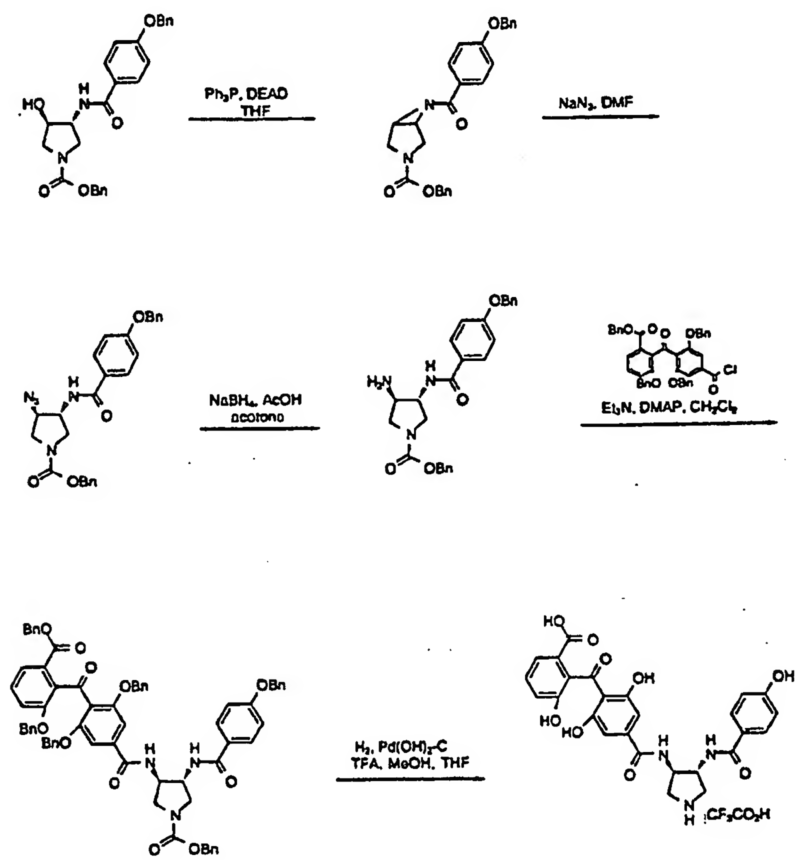
A solution of 68 mg (0.143 mmol) of 4-(6-benzyloxy-2-(benzyloxycarbonyl)benzoyl)benzoic acid in 5 mL of methylene chloride containing a trace (approximately 1 μL) of dimethylformamide was cooled to 0 °C. A 2.0 M solution of oxalyl chloride (0.11 mL, 0.22 mmol) was added, and the mixture was stirred under a nitrogen atmosphere for 2 h. An additional 0.17 mL of oxalyl chloride was added, and the mixture was stirred for an additional 2 h. The reaction

mixture was evaporated, and the residue was evaporated twice from 10 mL of methylene chloride. The residue was dissolved in 3 mL of methylene chloride, and was added to a solution of 69.6 mg (0.162 mmol) of *trans*-N-benzyl-3-(4-benzyloxybenzamido)-4-hydroxyazepine, 29.8 μL (0.17 mmol) of diisopropylethylamine, and 5.4 mg of DMAP in 5 mL of methylene chloride at 0 °C. The mixture was stirred at room temperature under a nitrogen atmosphere for 17 h, after which it was diluted with 30 mL of methylene chloride, washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated to give 146 mg of the crude product. Chromatography on silica gel eluting with 1/1 hexane - ethyl acetate gave 46 mg (37%) of Compound 634 as a yellow oil, which was taken directly to the next step.

Trans-N-Ethyl-4-(4-(2-carboxy-6-hydroxybenzoyl)benzoyloxy)-3-(4-hydroxybenzamido)azepine Trifluoroacetic Acid Salt Hydrate (COMPOUND 559)

A solution of 46 mg (0.052 mmol) of *trans*-N-benzyl-4-(4-(6-benzyloxy-2-(benzyloxycarbonyl)benzoyl)benzoyloxy)-3-(4-benzyloxybenzamido)azepine in 10 mL of ethanol was treated with 8.1 μL of trifluoroacetic acid, cooled to 0 °C, and 22 mg of moist 10% palladium hydroxide on carbon was added. The mixture was then stirred under an atmosphere of hydrogen for 19 h at room temperature. The mixture was filtered, evaporated, and the residue was chromatographed on a 21 x 250 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B:100% acetonitrile; gradient: 0-50% B over 60 min, flow: 15 mL/min). The pure fractions were pooled and evaporated and then lyophilized from water to give 3.8 mg (10%) of Compound 559 as a white fluffy solid. FABMS: *m/z* 547 (M + N).

Trans-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-hydroxycarbonylb nzoyl)-3,5-dihydroxybenzamido]pyrrolidine trifluoroacetic acid salt (COMPOUND 563)



640 563

A mixture of the benzyl ester (993 mg, 2.23 mmol, see Compound 589 for preparation) and triphenylphosphine (646 mg, 2.46 mmol) in THF (12 mL) was stirred and cooled to 5°C. To the resultant slurry was added diethylazodicarboxylate (428 mg, 2.46 mmol) in THF (3 mL) dropwise. The mixture was stirred at room temperature for 15 h and then evaporated. The residue was chromatographed (SiO_2, EtOAc: hexane = 1 : 2 followed by EtOAc: hexane : CH_2Cl_2 = 1 : 1 1) to give a white solid (793 mg, 83%).

A mixture of the previous product (689 mg, 1.61 mmol) and NaN_3 (209 mg, 3.22 mmol) in DMF (8 mL) was stirred at 65-70°C for 1 h and then diluted with THF (30 mL, containing 5 mL of Et_2O) after being cooled to room temperature. The mixture was washed with H_2O (5 x 10 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2, EtOAc: hexane: CH_2Cl_2 = 1 : 2: 1) to give a white solid (718 mg, 95%).

H_2O (1 mL), AcOH (0.5 mL), and zinc dust (312 mg, 4.8 mmol) were added, in that order, to a solution of the previous product (228 mg, 0.48 mmol) in EtOH (5 mL). The mixture was stirred at room temperature for 10 min., filtered, and evaporated. The residue was taken up with CH_2Cl_2 (20 mL), the insoluble material was filtered off, and the filtrate was evaporated. The remaining oil was chromatographed (SiO_2, EtOAc followed by acetone: EtOAc = 1 : 5) to give a colorless oil (122 mg, 57%).

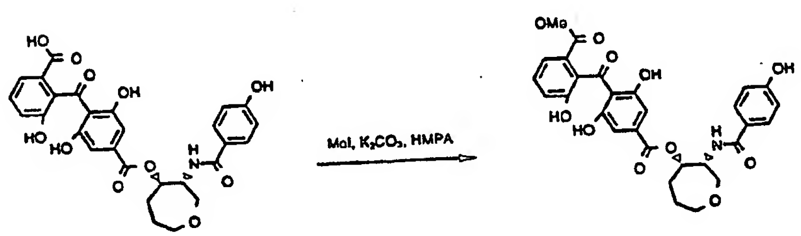
COMPOUND 640

Oxalyl chloride in CH_2Cl_2 (2 M, 0.26 mL, 0.53 mmol) was added dropwise to a solution of 4-(2-benzyloxy-6-benzyloxycarbonylbenzoyl)-3,5-dibenzyloxybenzoic acid (238 mg, 0.35 mmol) and a drop of DMF in CH_2Cl_2 (1 mL) at 5°C. The mixture was stirred at room temperature for 2 h, then evaporated to remove the solvent and excess oxalyl chloride. The residue was dried *in vacuo* for 1 h, dissolved in CH_2Cl_2 (0.5 mL), and added to a mixture of the previous product (122 mg, 0.27 mmol), Et_3N (55 mg, 0.54 mmol), and DMAP (ca. 3 mg, 0.027 mmol) in CH_2Cl_2 (1 mL) at 5°C. The mixture was stirred at room temperature for 17 h, diluted with CH_2Cl_2 (10 mL), washed with H_2O (3 x 10 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2, Et_2O: CH_2Cl_2: hexane = 1 : 1 : 1 followed by Et_2O: CH_2Cl_2: hexane = 2:2:1) to give a pale yellow oil (151 mg, 51%).

COMPOUND 563

Pd$(OH)_2$ on carbon(20 wt%, contains ≤50% moist, 19 mg, 0.014 mmol), trifluoroacetic acid (31 mg, 0.27 mmol), and MeOH (2 mL) was added to a solution of Compound 640 (150 mg, 0.14 mmol) in EtOAc (2 mL) and the mixture was stirred under 1 atm H_2 contained in a balloon at room temperature for 16 h. The mixture was filtered through Celite and the filtrate was evaporated to give an yellow solid (82 mg, 96%). IR (KBr, cm-1): 1675, 1636, 1606. FBMS: M/Z = 522 (M + 1).

Trans-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-methoxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxyl] perhydrooxepine (COMPOUND 567)



557 567

COMPOUND 567

A mixture of Compound 557 (20 mg, 0.037 mmol), iodomethane (0.009 mL. 0.148 mmol), and K_2CO_3 (10 mg, 0.074 mmol) in HMPA (0.15) mL was stirred at 40°C for a total of 3 h. Two additional portions of iodomethane (0.009 mL each)

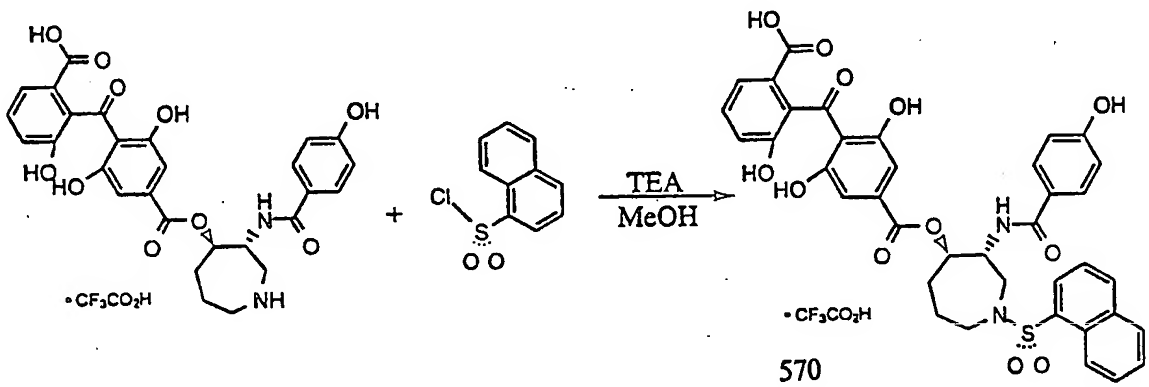
were added after the 1st and 2nd hour of stirring. EtOAc (10 mL) was added and the resultant mixture was washed with H_2O (3 x 10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. The residue was purified by preparative TLC (SiO_2, multi-elution with CH_2Cl_2 : 5% MeOH in EtOAc = 4: 1) to give a yellow solid (15 mg, 73%). IR (KBr, cm^{-1}):1716, 1635, 1607. FBMS: M/Z = 566 (M + 1).

(±)-*Anti*-4-[4-(2-Methoxycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxy-benzamido]hexahydro-3-(4-hydroxybenzamido)azepine, trifluoroacetic acid salt (COMPOUND 568)

An ice-cooled solution of (±)-*anti*-4-[4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzamido]hexahydro-3-(4-hydroxybenzamido)azepine, trifluoroacetic acid salt Compound 515 19 mg, 0.026 mmol) in anhydrous methanol (3 mL) in a 2-neck flask equipped with a thermometer was treated with a stream of hydrogen chloride gas. The pot temperature immediately rose to 50°C, and the stream of HCl was continued until the temperature had returned to 25°C (approx. 2.5 min). The solution was refluxed under a drying tube for 1 h, 40 min, then concentrated *in vacuo*. The residue was dissolved in N,N-dimethylformamide (0.3 mL) and loaded on HPLC; conditions: A: 0.1%TFA / 5%CH_3CN / H_2O, B: CN_3CN, 100% A to 50% A: 50% B over one hour, 15 min, 21 x 250 cm C_{18} column. Fractions (one/min) 28 - 31 were combined, partially concentrated *in vacuo*, and freeze-dried overnight to afford (±)-anti-4-[4-(2-methoxycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxybenzamido]-hexahydro-3-(4-hydroxybenzamido)azepine, trifluoroacetic acid salt Compound 568, 13.7 mg, 68%) as a voluminous pale yellow solid; mp 200 -210°C (dec). R_f (69:30:1 CH_2Cl_2 / MeOH / NH_4OH) 0.48; IR (KBr): 1676, 1636, 1607 cm^{-1}; ^1H NMR (d_6-DMSO) δ 1.67 (s, 2H), 10.11 (s, 1H), 10.02 (s, 1H, 8.80 - 9.05 (br s, 2H), 8.68 (d, 1H, J = 8 Hz), 8.31 (d, 1H, J = 8 Hz), 7.70 (d, 2H, J = 9Hz), 7.42 (d, 1H, J = 8Hz), 7.3I (t, 1H, J = 8Hz), 7.14 (d, 1H, J = 8Hz), 6.84 (d, 2H, J = 9 Hz), 6.70 (s, 2H), 4.30 (m, 2H), 3.65 (s, 3H), 3.20 3.60 (m, 3H), 3.00 - 3.20 (m, 1H), 1.80 - 2.05 (m, 4H);

mass spectrum (FAB) m/z 564. Anal. Calcd. for $C_{29}H_{29}N_3O_9$ • 1.4($C_2HO_2F_3$) • 3(H_2O): C, 49.14; H, 4.72; N, 5.41. Found: C, 49.21; H, 4.38; N, 5.44.

(±)-*Trans*-4-[4-(2-Hydroxycarbonyl-6-hydroxybenzoyl)-3,5 dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)-1-(1-naphthalene sulfonyl)azepine (COMPOUND 570)

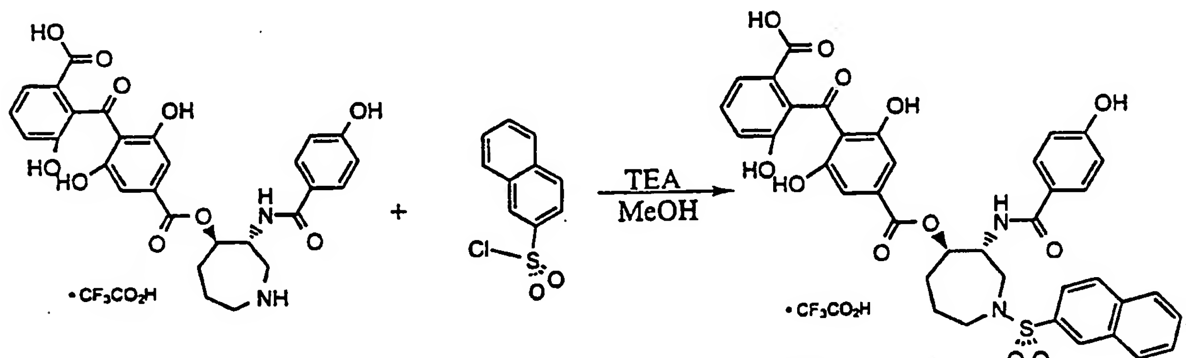


570

Racemic balanol (preparation described in preparation of Compound 508 100 mg, 147 µmol) was dissolved in methanol (1 mL) and treated with triethylamine (204 mL, 1.47 µmol) and 1-naphthalene sulfonyl chloride (49.8 mg, 219.7 µmol) in methylene chloride (1 mL). After stirring at room temperature for 3 h, the mixture was concentrated under vacuum to a yellow film. The residue was dissolved in DMF (2 mL) and chromatographed on a Dynamax®-60 C_{18} column (41 mm ID x 25 cm length) using a linear gradient from 100% A (0.1% TFA and 5% acetonitrile in water) to 100% B (pure acetonitrile) over 60m at 25 mL/min. The clean product, which eluted in 40 m, was freeze-dried to give a yellow powder (36 mg, 33%): m.p. 176-178° C dec; ^{1}H-NMR (DMSO, 300 MHz) δ 61.68-2.09 (4H, m), 3.27-3.52 (3H, m), 3.67 (1H, d, 7 = 3.3 Hz), 4.29-4.38 (1H, m), 5,12-5.22 (1H, m), 6.78 (4H, t), 7.04 (1H, d, 7 = 8

Hz), 7.27 (1H, t), 7.36 (1H, d, 7 = 8 Hz), 7.60-7.77 (5H, m), 8.04-8.12 (2H, m), 8.57 (1H, d, 7 = 8 Hz), 9.85 (1H, s), 9.95 (1H, s), 11.63 (1H,s); IR (KBr): cm^{-1} 3399, 3273, 3083, 2946, 2876, 2682, 2360, 2340, 1705, 1635, 1607, 1541, 1506, 1460, 1425, 1367, 1343, 1278, 1238, 1202, 1176, 1157, 1130, 1065, 990, 920, 846, 803, 766, 678, 670, 583, 544, 519. Anal. Calcd. for $C_{38}H_{32}N_2O_{12}S \cdot 2H_2O \cdot .15TFA \cdot .16CH_3CN$: C, 57.95; H, 4.61; N, 3.77; S, 4.01. Found: C, 57.94; H, 4.33; N, 3.76; S, 3.82. IRMS (FAB) m/z 741.1.

(±)-*Trans*-4-[4-(2-Hydroxycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)-1-(2-naphthalene sulfonyl)azepine (COMPOUND 571)

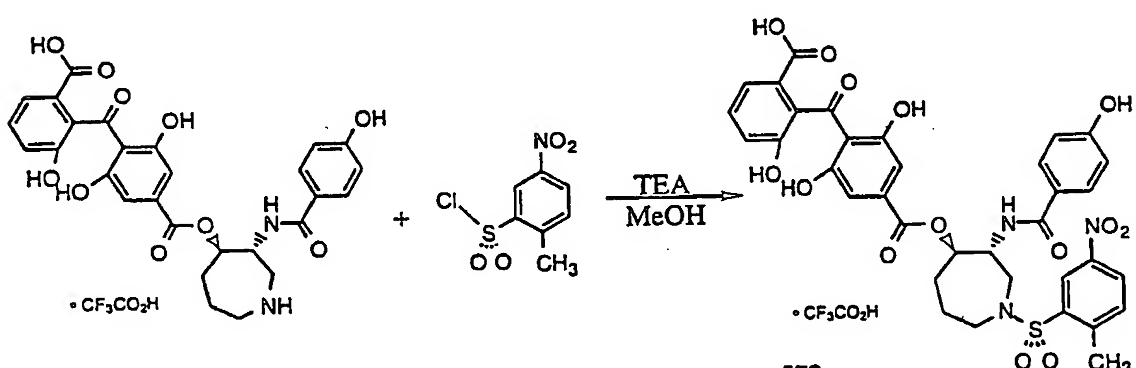


571

Racemic balanol (preparation described in preparation of Compound 508; 100 mg, 147 µmol) was dissolved in methanol (1 mL) and treated with triethylamine (204 mL, 1.47 µmol) and 2-naphthalene sulfonyl chloride (49.8 mg, 219.7 µmol) in methylene chloride (1 mL). After stirring at room temperature for 3 h, the mixture was concentrated under vacuum to a yellow film. The residue was dissolved in DMF (2 mL) and chromatographed on a Dynamax -60 C_{18} column (41 mm ID x 25 cm length) using a linear gradient from 100% A (0.1% TFA

and 5% acetonitrile in water) to 100% B (pure acetonitrile) over 60m at 25 mL/min. The clean product, which eluted in 43 m, was freeze-dried to give a yellow powder (30 mg, 28%): m.p. 187-190° C dec; 1H-NMR (DMSO, 300 MHz) δ 61.62-2.07 (4H,m), 3.20-3.40 (3H,m), 3.55 (1H, d, 7 = 3.3 Hz), 4.28-4.37 (1H, m), 5.12 (1H, t), 6.77 (4HN, t), 7.03 (1H, d, 7 = 8 Hz), 7.26 (1H, t), 7.35 (1H, d, 7 = 8 Hz), 7.60-7.72 (4H, m), 7.82 (1H, d, 7 = 8 Hz), 8.05 (1H, d, 7 = 8 Hz), 8.11-8.23 (3H, m), 8.49 (1H, s), 9.84 (IN, s), I 1.62 (IN,s); IR (103r): cm-1 3391, 3273, 3080, 2947, 2875, 2361, 2340, 1707, 1635, 1607, 1541, 1505, 1461, 1425, 1368, 1324, 1236, 1202, 1176, 1153, 1130, 1104, 1073, 920, 851, 816, 760, 717, 679, 668, 656, 614, 546, 475. Anal. Calcd. for $C_{38}H_{32}N_2O_{12}S \circ 2.3H_2O \circ .11TFA \circ .2CHN_3CN$: C, 57.77; H, 4.68; N, 3.84; S, 3.99. Found: C, 57.77; H, 4.29; N, 3.90; S, 3.92. IRMS (FAB) m/z 740.9.

(±)-*Trans*-4-[4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)-1-(2-methyl-5-nitrobenzenesulfonyl)azepine, trifluoracetic acid salt (COMPOUND 572)



572

Racemic balanol (100 mg, 147 μmol) was dissolved in methanol (1 mL) and treated with triethylamine (204 ml, 1.47 μmol) and 2-methyl-5-nitrobenzene sulfonyl chloride (51.8 mg, 219.7 μmol) in methylene chloride (1 mL). After stirring at

room temperature for 3 h, the mixture was concentrated under vacuum to a yellow film. The residue was dissolved in DMF (2 mL) and chromatographed on a Dynamax -60 C_{18} column (41 mm ID x 25 cm length) using a linear gradient from 100% A (0.1% TFA and 5% acetonitrile in water) to 100% B (pure acetonitrile) over 60m at 25 mL/min. The clean product, which eluted in 34 m, was freeze-dried to give Compound 572 as a yellow powder (20 mg, 18%): m.p. 176-178° C dec; ^{1}H-NMR (DMSO, 300 MHz) δ 61.81-2.03 (3H, m), 2.14-2.27 (1H, m), 2.82 (3H, s), 4.45-4.60 (1H, m), 5.22-5.34 (1H, m), 6.78 (2H, s), 7.07 (1H, d, J = 8 Hz), 7.20-7.37 (3H, m), 7.42 (1H, d, J = 8 Hz), 7.78 (2H, d, 7 = 8.5 Hz), 8.39 (1H, s), 8.57 (1H, d, 7 = 8 Hz), 8.88 (1H, d, 7 = 8 Hz), 9.90 (1HN,s), 11.69 (1H, s); IR (KBr): cm^{-1} 3428, 3275, 3257, 3106, 3083, 2978, 2872, 1675, 1653, 1636, 1605, 1560, 1529, 1497, 1425, 1354, 1288, 1231, 1200, 1142, 1104, 1061, 989, 958, 920, 894, 869, 800, 764, 739, 724, 594, 457. Anal. Calcd. for $C_{35}H_{31}N_3O_{14S}S \cdot 1.5H_2O \cdot 1.1TFA$: C, 49.53; H, 3.92; N, 4.66; 5,3.55. Found: C, 49.53; H, 3.81; N, 4.60; 5,3.24. IRMS (FAB) m/z 749.8.

(±)-*Anti*-3-[4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyl-oxyl-1-[N(1,1-dimethylethyl)iminomethyl]-4-(4-hydroxybenzamido)-pyrrolidine, trifluoroacetic acid salt (COMPOUND 575)

(±)-*Anti*-1-[N(1-1-dimethylethyl)iminomethyl]-3-hydroxy-4-(4-hydroxybenzamido)pyrrolidine

A suspension of (±)-*anti*-3-hydroxy-4-(4-hydroxybenzamido)pyrrolidine (0.312 g, 1.0 mmol) in toluene/N,N-dimethylformamide (3:2,2.5 mL) under nitrogen was treated with N'-*t*-butyl-N,N-dimethylformamidine (Aldrich, 0.50g, 3.9 mmol), then with ammonium chloride (20 mg, 0.37 mmol). The mixture was heated to 90°C for 18 h, diluted with 0.5 N sodium hydroxide (10 mL), and the aqueous solution was extracted with toluene (2x25 mL) containing some 2-propanol. The combined organic extracts were washed with water (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Silica gel

chromatography (eluted with 2:2:1 ethyl acetate/ triethylamine) afforded, after reconcentration with toluene, (±)-*anti*-1-[N-(1,1-dimethylethyl)iminomethyl]-3-hydroxy-4-(4-hydroxy-benzamido)pyrrolidine (186 mg, 47%) as a colorless solid.

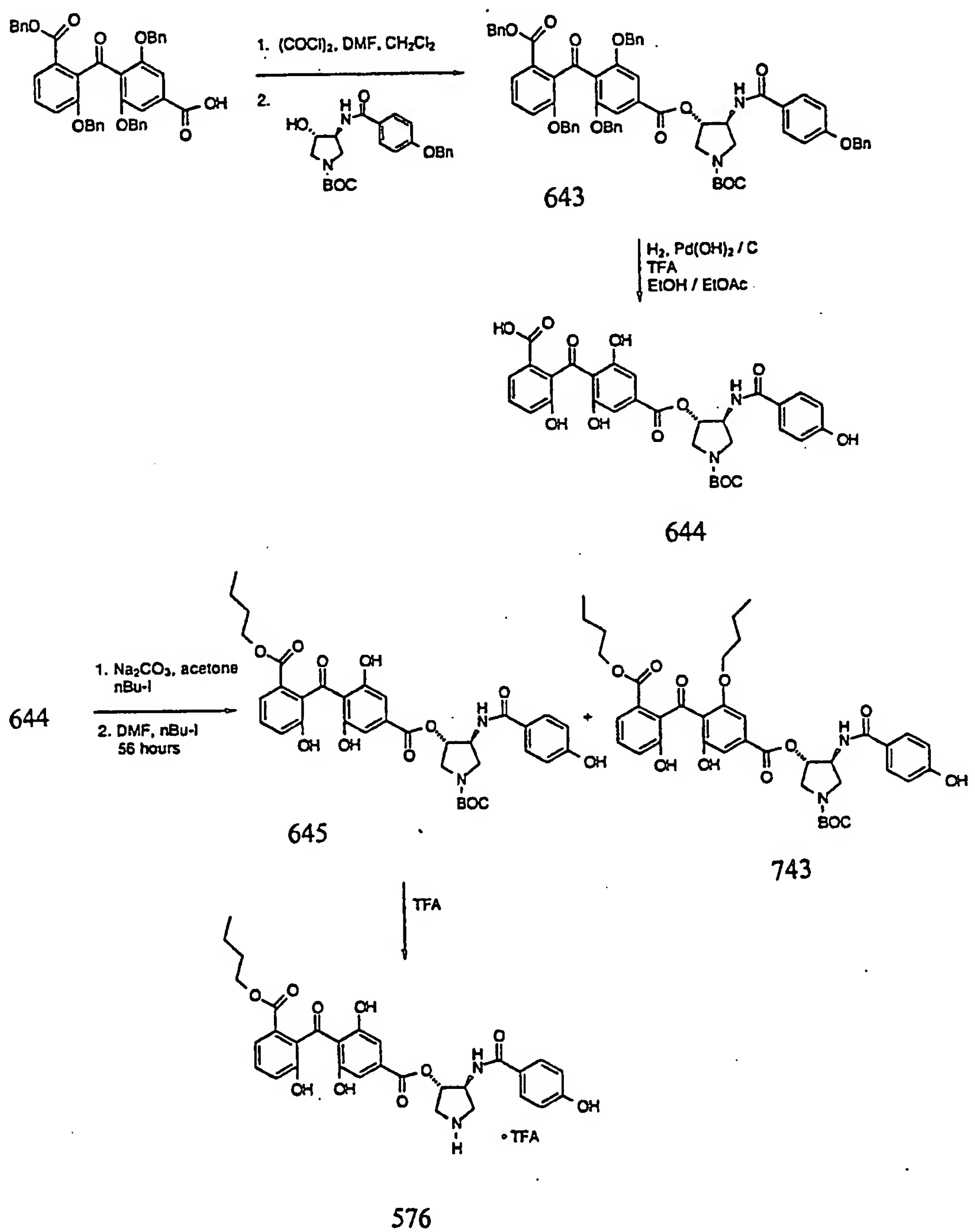
(±)-*Anti*-3-[4-(2-Carbophenylmethoxy-6-phenylmethoxybenzoyl)-3,5-bis(phenylmethoxy)benzoyloxy]-1-[N-(1,1-dimethylethyl)-iminomethyl]-4-(4-phenylmethoxybenzamido)pyrrolidine (COMPOUND 642)

A solution of 4-(carbophenylmethoxy-6-phenylmethoxybenzoyl)-3,5-bis(phenylmethoxy)benzoic acid (0.19g, 0.28 mmol) in anhydrous methylene chloride (2.0 mL) was treated with N,N-dimethylformamide (3 drops), then with 2.0 N oxalyl chloride/methylene chloride (Aldrich, 0.25 mL, 0.50 mmol), and was stirred for one hour under nitrogen. The solution was concentrated *in vacuo*, placed under high vacuum for one hour, then taken up in THF/DMF (3:2, 1.25 mL) under nitrogen. Triethylamine (0.50 mL) and 4-dimethylaminopyridine (35 mg) were added, followed closely by (±)-*anti*-[N-(1,1-dimethylethyl)imino-methyl]-3-hydroxy-4-(4-hydroxybenzamido)pyrrolidine (80 mg, 0.20 mmol). The solution was stirred at room temperature for 18h, then diluted with toluene (20 mL) containing some 2-propanol. The organic solution was washed with 0.5 N sodium hydroxide (10 mL), then water (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Silica gel chromatography (eluted with 90 : 5 : 5 ethyl acetate/2-propanol/triethylamine) afforded (±)-anti-3-[4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)-3,5-bis(phenylmethoxy)benzoyloxy]-1-[N-(1,1-dimethylethyl) iminomethyl]-4-(4-phenylmethoxybenzamido)pyrrolidine (87 mg, 41%) as a pale yellow viscous oil.

(±)-*Anti*-3-[4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxybeflzoyl-oxy]-t-[N-(1,1-dim thylethyl)iminomethyl]-4-(4-hydroxybenzamido)-pyrrolidine, triflrnoroacetic acid salt (COMPOUND 575)

A solution of (±)-*anti*-3-[4-(2-carbophenylmethoxy-6-phenylmethoxybenzoyl)-3,5-bis(phenylmethoxy)benzoyloxy]-1-[N-(1,1-dimethylethyl)iminomethyl]-4-(4-phenylmethoxybenzamido)pyrrolidine (87 mg, 0.082 mmol) in ethanol (20 mL) in a 500 mL Parr bottle was treated with trifluoroacetic acid (50 μL) and purged with nitrogen. Pearlman's catalyst (145 mg) was added, and the vessel was immediately charged with hydrogen (45 psi) on a Parr apparatus and shaken for 40h. The bottle was carefully evacuated of hydrogen, the solution was filtered through celite, and the filter cake was rinsed with ethanol with care taken not to allow it to dry. The filtrate was concentrated *in vacuo* and the residue was dissolved in N,N-dimethylformamide (0.3 mL) and loaded onto HPLC; conditions: A- 0.1%TFA/5%CH_3CN/H_2O, B- CH_3CN, 100% A to 50:50 A:B over one hour, 15 mL/min, 21 x 250 mm C18 column. Fractions (one/min) 29 - 33 were combined, partially concentrated *in vacuo*, and freeze dried overnight to afford (±)-*anti*-3-[4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyl-oxy]-1-[N-(1,1-dimethylethyl)iminomethyl]-4-(4-hydroxybenzamido)-pyrrolidine, trifluoroacetic acid salt (20.4 mg, 32%) as a voluminous beige solid; mp 200 - 208°C (dec). R_f (12:1:1 n-BuOH/AcOH/H_2O on silica) 0.60; IR (KBr) 1697, 1640, 1607 cm^{-1}; ^{1}H NMR (d_6-DMSO) δ 12.90 (br s, 1H), 11.75 (br s, 2H), 10.10 (s, 1H), 9,89 (s, 1H), 9.06 (m, 1H), 8.54 (m, 1H), 8.31 (m, 1H), 7.75 (m, 2H), 7.37 (d, 1H, J = 8 Hz), 7.29 (t, 1H, J = 8 Hz), 7.06 (d, 1H, J = 8 Hz), 6.80 -6.90 (m, 4H), 5.40 - 5.50 (m, 1H), 4.60 - 4.73 (m, 1H), 4.10 - 4.30 (m, 1H), 3.85 -4.05 (m, 2H), 3.60 - 3.70 (m, 1H), 1.33 (s, 9N); mass spectrum (FAB): m/z 606. Anal. Calcd. for $C_{31}H_{31}O_{10}$ • $C_2HO_2F_3$ • $3H_2O$ • 0.25(C_2H_3N): C, 51.33; H, 4.98; N, 5.81. Found: C, 50.94; H, 4.90; N, 5.97.

Trans-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-butoxycarbonylbenzoyl)-3,5-dihyrdroxybenzoyloxy]pyrrolidin trifluoroacetic acid salt (COMPOUND 576)



Trans-N-t-butoxycarbonyl-3-(4-benzyloxybenzamido)-4-[4-(2-benzyl xy-6-benzyloxycarbonylbenzoyl)-3,5-dibenzyloxybenzoyloxy] pyrrolidin (COMPOUND 643)

4-[4-(2-benzyloxy-6-benzyloxycarbonylbenzoyl)]-3,5-dibenzyloxybenzoic acid (1.47 mmol, 996 mg) and 15 mL anhydrous CH_2Cl_2 in a dry round-bottom flask were cooled in an ice/water bath under N_2. To this was added oxalyl chloride (2.87 mol, 0.25 ml and 5 drops of DMF. This was allowed to stir for 2 hours while the bath melted. TLC (2:1 hexanes:EtOAc) indicated complete formation of the acid chloride. The solvent was removed *in vacuo*.

In a 200 mL dry round-bottom flask was added *trans*-N-*t*-butoxycarbonyl-3-(4-benzyloxybenzamido)-4-hydroxypyrrolidine (1.26 mmol, 500 mg) in 12 mL anhydrous CH_2Cl_2 under N_2. To this was added triethylamine (3.6 mmol, 0.5 mL) and DMAP (150 mg). A solution of the acid chloride generated above in 10 mL anhydrous CH_2Cl_2 was added *via* cannula. This was allowed to stir under N_2 at room temperature overnight. The reaction mixture was then diluted with CH_2Cl_2, washed with sat. $NaHCO_3$, brine, then dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography using 5% acetone / CH_2Cl_2 as the eluent. (COMPOUND 643) (1.08 mmol, 1.15 g) was obtained in 86% yield.

Trans-N-t-butoxycarbonyl-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-carboxybenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine (COMPOUND 644)

To a 500 mL 3-neck round-bottom flask was added *trans*-N-*t*-butoxycarbonyl-3-(4-benzyloxybenzamido)-4-[4-(2-benzyloxy-6-benzyloxycarbonylbenzoyl)-3,5-dibenzyloxybenzoyloxy]pyrrolidine (Compound 643, 1.02 mmol, 1.08 g) in 17 mL EtOAc and 70 mL ethanol under H_2. To this was added trifluoroacetic acid (2.55 mmol, 0.20 mL) and $Pd(OH)_2$ / C (730 mg) followed immediately by introduction of H_2 at 1 atmosphere. After a reaction time of 3.5 hours, the

reaction was flushed with N_2 and filtered through Celite, rinsing with ethanol. Following concentration *in vacuo*, crude product (Compound 644, 644 mg) was obtained in quantitative yield. A small portion was purified *via* HPLC (21 x 250 mm C18 column, gradient %B = 0 to 50 over 60 min. where A = 0.1% TFA, 5% CH_3CN in water and = CH_3CN, 15 mL/min. UV = 254 nm) for characterization and the remainder was used crude in subsequent reactions. m.p. 196°C (dec). IR (KBr) 3375(br), 2978, 1704, 1660, 1637, 1607, 1506, 1426, 1368, 1231 cm^{-1}. ^1H NMR CD_3OD, δ 8.52 (d, 1H), 7.72 (d, 2H), 7.49 (d, 1H), 7.26 (t, 1H), 7.01 (d, 1H), 6.91 (s, 2H), 6.80 (d, 2H), 5.40 (m, 1H), 4.63 (m, 1H), 3.87 (m, 2H), 3.50 (m, 2H), 1.47 (s, 9H). IRM (M + I) cacld for $C_{31}H_{31}N_2O_{12}$ 623.2, found 623.2. Anal. Calcd for $C_{31}H_{30}N_2O_{12} \circ 1.5\ H_2O$: C, 57.317; H, 5.120; N, 4.312. Found: C, 57.26; H, 5.18; N, 4.47.

Trans-N-*t*-butoxycarbonyl-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-butoxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy] pyrrolidine (COMPOUND 645)

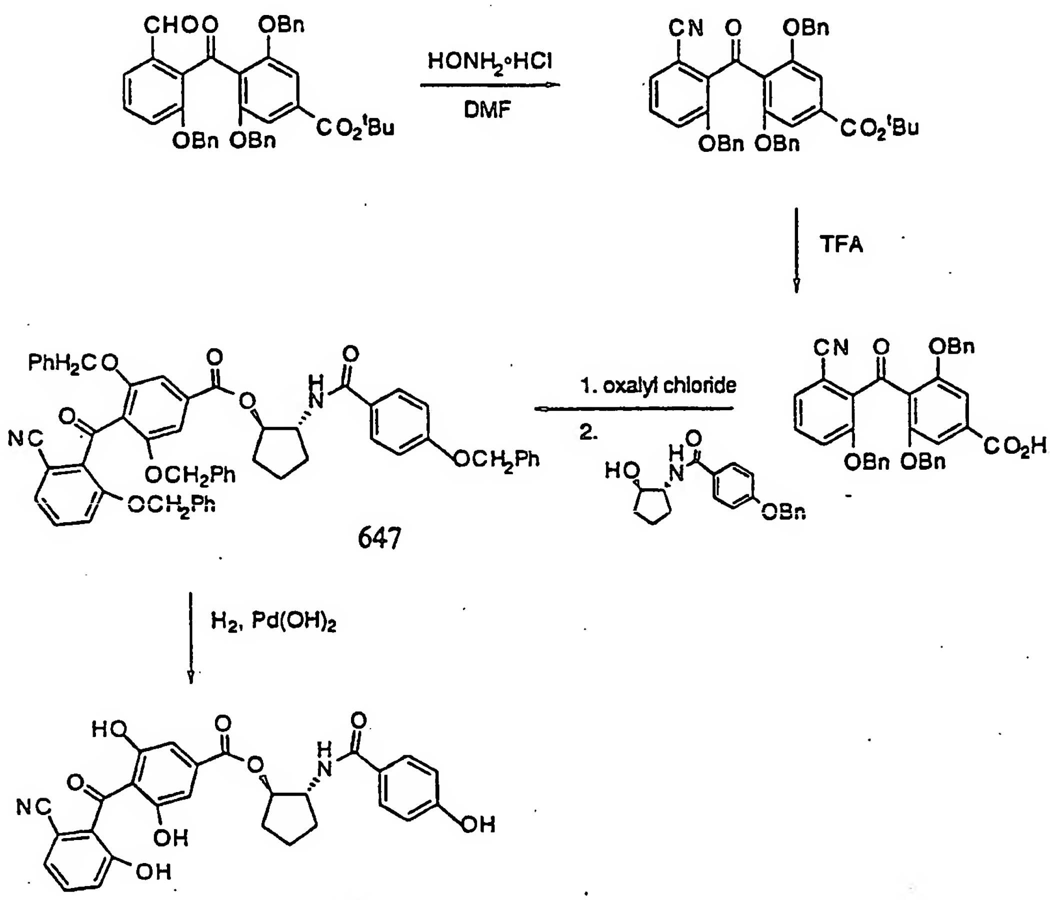
To a 25 mL round-bottom flask was added *trans*-N-*t*-butoxycarbonyl-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-carboxybenzoyl)-3,5-dihydroxybenzoyloxy]-pyrrolidine (Compound 644, 0.17 mmol, 104 mg) in 5 mL acetone. To this was added Na_2CO_4 (0.27 mmol, 29 mg) and 1-iodobutane (0.88 mmol, 0.1mL). This was allowed to stir under N_2 for 18 hours at which time TLC (EtOAc) showed no reaction taking place. Next was added additional 1-iodobutane (1.7 mmol, 0.2 mL) and 2 mL DMF to increase solubility of the Na_2CO_3. The reaction stirred under N_2 for an additional 38 hours at which time the reaction mixture was diluted with EtOAc and washed with brine 4 times. The crude product was purified *via* flash column chromatography (eluent, 2:1 CH_2Cl_2:acetone to 1:1 CH_2Cl_2:MeOH) at which time 2 products were identified (Compound 645 and Compound 743). Further purification *via* HPLC (21 x 250 mm C18 column, gradient %B = 0 to 100 over 60 min. where A = 0.1% TFA, 5% CN_3CN in water and B = CH_3CN, 15 mL/min. UV = 254 nm) was necessary to isolate *trans*-N-*t*-butoxycarbonyl-3-

(4-hydroxybenzamido)4-[4-(2-hydroxy-6-butoxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine (Compound 645, 20 mg, 36% yield) from *trans*-N-t-butoxycarbonyl-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-butoxycarbonylbenzoyl)-3-butoxy-5-hydroxybenzoyloxy]pyrrolidine (Compound 743, 32 mg, 25% yield).

Trans-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-butoxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine trifluoroacetic acid salt (COMPOUND 576)

Trans-N-*t*-butoxycarbonyl-3-(4-hydroxybenzamido)-4[4-(2-hydroxy-6-butoxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine (Compound 645, 0.044 mmol, 30 mg) was dissolved in 0.6 mL neat trifluoroacetic acid and allowed to stir at room temperature under N_2 for 45 minutes at which time TLC (75% CH_2Cl_2, 24% MeOH, 1% (10% aq.) NH_4OH) indicated the reaction was complete. This was diluted with toluene and concentrated *in vacuo* to yield 29.8 mg (98% yield) of crude product. Purification *via* HPLC (21 x 250 mm C18 column, gradient %B = 0 to 100 over 60 min. where A = 0.1% TFA, 5% CH_3CN in water and B = CH_3CN, 15 mL/min. UV = 254 nm) yielded *trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-butoxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine trifluoroacetic acid salt (Compound 576, 28 mg, 92% yield) as a yellow solid. m.p. 140-146°C (dec.). IR (KBr) 3270 (br), 2964, 1677, 1607, 1508, 1426, 1371, 1298, 1201 cm^{-1}. ^1H NMR, DMSO-d_6, δ, 11.73 (s, 2H), 10.11 (s, 1H), 10.00 (s, 1H), 8.50 (d, 1H), 7.73 (d, 2H), 7.41 (d, 1H), 7.33 (t, 1H), 7.10 (d, 1H), 6.94 (s, 2H), 6.82 (d, 2H), 5.50 (m, 1H), 4.58 (m, 1H), 4.07 (t, 2H), 3.71 (m, 2H), 3.50 (m, 2HN), 1.43 (m, 2H), 1.22 (m, 2), 0.80 (t, 3HN). IRMS (M + 1) calcd for $C_{30}H_{31}N_2O_{10}$ 579.20, found 579.1. Anal. Calcd for $C_{30}N_{30}N_2O_{10}$ • $C_2HF_3O_2$ • 1.5 H_2O: C, 53.41; H, 4.76; N, 3.89. Found: C, 53.66; H, 4.52; N, 3.94.

(±)-*Trans*-2-[4-(6-hydroxy-2-nitrilobenzoyl]-3,5-dihydroxybenz yloxy)-1-(4-hydroxybenzamido)cyclopentane (COMPOUND 578)



578

[4-(2-benzyloxy-6-nitrilobenzoyl)-3,5-dibenzyloxy]benzoic acid, tert-butyl ester

To a solution of the depicted benzophenone (2.00 g, 3.15 mmol) in dimethylformamide (15.8 mL) was added hydroxylamine hydrochloride (438 mg, 6.30 mmol, 2.0 eq). The system was heated with stirring at 50-55°C for 16 h, then

allowed to cool. The yellow solution was poured onto ice, and stirred while the ice was allowed to melt. The resulting white solid was collected by filtration, washed with diethyl ether (30 mL), and dried under vacuum to provide the product (1.29 g, 65%) as a white solid: m.p. 139-140°; ^1H NMR (300 MHz, $CDCl_3$) δ 7.2-7.4 (m, 9H), 7.0-7.2 (m, 9H), 6.84 (d, J = 9.0 Hz, 2H), 4.85 (s, 4H), 4.71 (s, 2H), 1.63 (s, 9H).

[4-(2-benzyloxy-6-nitrilobenzoyl)-3,5-dibenzyloxy]benzoic acid

To a solution of the previous reaction product (293 mg, 0.515 mmol) in CH_2Cl_2 (5.15 mL) was added trifluoroacetic acid (794 µL, 10.3 mmol, 20 eq) dropwise, during which time the solution turned orange. The mixture was stirred at room temperature 4 h, evaporated, then evaporated from toluene (8 mL) to give an orange powder. The solid was triturated with Et_2O (8 mL), and the light yellow solid collected and dried (161 mg, 60%): IR (KBr) 3481, 2230, 1675, 1582, 1120, 742, 698 cm^{-1}.

(±)-*Trans*-2-[4-(6-benzyloxy-2-(nitrilo)benzoyl]-3,5-dibenzyloxybenzoyloxy)-1-(4-benzyloxybenzamido)cyclopentane (COMPOUND 647)

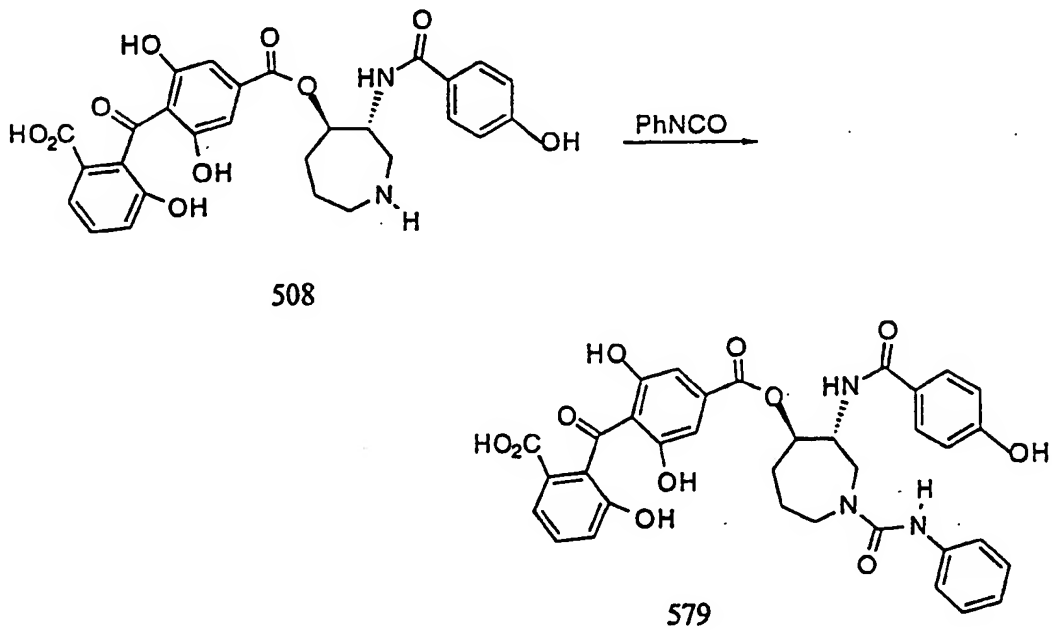
To a 0°C solution of the previous reaction product (161 mg, 0.283 mmol) in CH_2Cl_2 (5.7 mL) were added DMF (1 drop) then oxalyl chloride (0.28 mL of a 2.0 M solution in CH_2Cl_2, 0.566 mmol, 2.0 eq). The orange solution was stirred at 0°C under N_2 for 1 h, then evaporated down and placed on the vacuum pump for 30 min. To a slurry of this light yellow powder in CH_2Cl_2 (8.5 mL) were added diisopropylethyl amine (59 µL, 0.34 mmol, 1.2 eq), 4-N,N-dimethylaminopyridine (35 mg, 0.283 mmol, 1.0 eq) then 2-(4-benzyloxybenzamido-2-hydroxy cyclopentane (88 mg, 1.0 eq). The mixture was stirred at room temperature under N_2 14 h. The light yellow solution was diluted with CH_2Cl_2 (20 mL), washed with 1N KOH (30 mL) then 5% HCl (30 mL). The organic layer was dried

($MgSO_4$), filtered and evaporated to a tan foam which was purified by flash column chromatography on silica gel (2:1 hexane:ethyl acetate) to provide Compound 647 (158 mg, 65%) as a white foam: ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 8.8 Hz, 2H), 6.95-7.5 (m, 18H), 6.96 (d, J = 8.9 Hz, 2H), 6.88 (d, J = 6.7 Hz, 1H), 6.6.78 (d, J = 7.0 Hz, 2H), 5.32 (q, J = 6.0 Hz, 1H), 5.09 (s, 2H), 4.83 (s, 4H), 4.67 (s, 2H), 2.4-2.55 (m, 1H), 2.2-2.4 (m, 1H), 1.8-2.0 (m, 2H), 1.6-1.8 (m, 1H), 1.3-1.4 (m, 1H).

(±)-*Trans*-2-[4-(6-hydroxy-2-nitrilobenzoyl]-3,5-dihydroxybenzoyloxy)-1-(4-hydroxybenzamido)cyclopentane (COMPOUND 578)

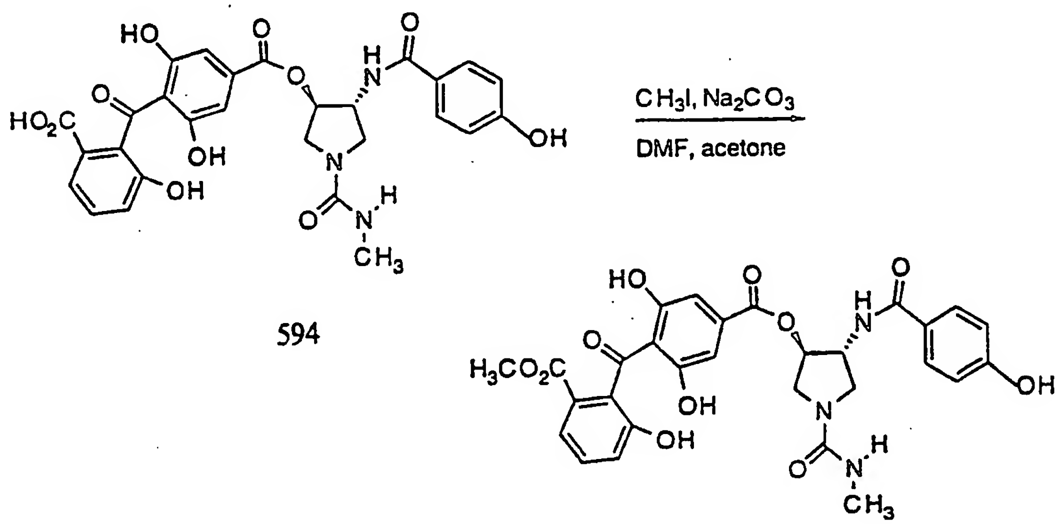
To a round bottom flask containing Compound 647 (123 mg, 0.143 mmol) and $Pd(OH)_2$ (31 mg of a 20% powder) was added THF (12.9 mL). The flask was evacuated and filled with H_2 twice then allowed to stir under H_2 (1 atm) 16 h. The solution was filtered through Celite, washed through with CH_2Cl_2 (20 mL), combined with a previous run (identical conditions, 0.029 mmol scale), and evaporated. The golden oil was purified by reverse phase HPLC (C18 column), then the product-containing fractions were combined and re-purified by flash column chromatography on silica gel (95:5 CH_2Cl_2:MeOH) to provide Compound 578 (48 mg, 56%) as a yellow powder after lyophilization from MeOH and H_2O: m.p. 125-130° (dec); ^1H NMR (300 MHz, CD_3OD) δ 7.48 (d, J = 8.7 Hz, 2H), 7.22 (dd, J = 8.1, 7.9 Hz, 1H), 7.04 (d, J = 6.6 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.77 (s, 2H), 6.60 (d, J = 8.8 Hz, 2H), 5.08 (dt, J = 5.3, 5.2 Hz, 1H), 4.30 (dt, J = 13.6, 8.1 Hz, 1H), 2.0-2.1 (m, 2H), 1.65-1.75 (m, 2H), 1.4-1.65 (m, 2H); IR (KBr) 3386, 2234, 1708, 1609, 1429, 1240 cm^{-1}; MS m/e calc'd for $C_{27}H_{23}N_2O_8$ (M^+ + 1): 503.1454, found 503.1380; Analysis calc'd for $C_{27}H_{22}N_2O_8 \circ H_2O$: C, 62.30; H, 4.65; N, 5.38; found: C, 62.30; H, 4.70; N, 5.29.

(±)-*Trans*-4-[4-(2-Carboxy-6-hydr xybenzoyl)-3,5-dihydroxybenz yloxy]-3-(4-hydroxybenzamido)-1-(phenylaminocarbonyl)azepine (COMPOUND 579)



To a solution of racemic balanol (Compound 508, 141 mg, 0.212 mmol) in pyridine (1.8 mL) was added phenyl isocyanate (30 μL, 0.36 mmol, 1.7 eq). The yellow mixture was stirred at room temperature 3 h, then evaporated. A portion of the material was purified by reverse phase HPLC (C18 column) to provide the racemic product: m.p. 174-183° (dec); ^{1}H NMR (300 MHz, CD_3OD) δ 7.48 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 7.7 Hz, 2H), 7.27 (d, J = 7.7 Hz, 1H), 7.0-7.1 (m, 3H), 6.75-6.85 (m, 2H), 6.70 (s, 2H), 6.59 (d, J = 8.7 Hz, 2H), 4.95-5.05 (m, 1 H), 4.0-4.1 (m, 1H), 3.0-3.2 (m, 2H), 3.2-3.3 (m, IH), 2.0-2.1 (m, IH), 1.5-1.9 (m, 4H); IR (KBr) 3367, 1707, 1607, 1502, 1236 cm^{-1}; MS *m/e* calc'd for $C_{35}H_{32}N_3O_{11}$ (M^+ + 1): 670.2032, found 670.2082.

(±)-*Trans*-4-[4-(2-Methylcarboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)-1-(methylaminocarbonyl)pyrrolidine (COMPOUND 580)



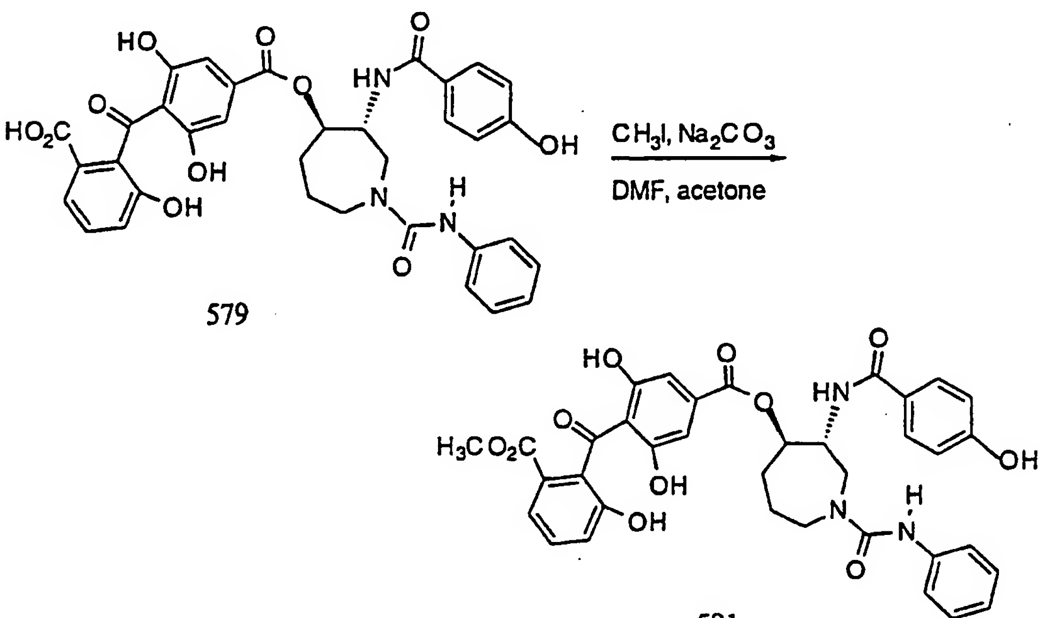
594

580

To a solution of Compound 594 (44 mg, 0.076 mmol) in dimethylformamide (1.9 mL) and acetone (1.9 mL) were added Na_2CO_3 (12 mg, 0.11 mmol, 1.5 eq) then iodomethane (142 μL, 2.28 mmol, 30 eq). The mixture was stirred at room temperature 2 h then diluted with ethyl acetate (25 mL) and washed with H_2O (2 x 30 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. Purification of the two spots by reverse phase HPLC (C18 column) provided the title ester (6.3 mg, 14%) as a yellow powder after lyophilization: ^{1}H NMR (300 MHz, CD_3OD) δ 7.52 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 7.6 Hz, 1H), 7.08 (dd, J = 7.9, 8.0 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.72 (s, 2H), 6.61 (d, J = 8.7 Hz, 2H), 5.2-5.3 (m, 1H), 4.4-4.5 (m, 1H), 3.6-3.75 (m, 2H), 3.2-3.4 (m, 2H);

MS m/e calc'd for $C_{29}H_{28}N_3O_{11}$ (M^+ + 1): 594.1724, found 594.1714.

(±)-*Trans*-4-[4-(2-Methylcarboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)-1-(phenylaminocarbonyl)azepine (COMPOUND 581)



To a solution of Compound 579 (0.14 mmol) in dimethylformamide (3.4 mL) and acetone (3.4 mL) were added Na_2CO_3 (22 mg, 0.21 mmol, 1.5 eq) then iodomethane (260 µL, 4.1 mmol, 30 eq). The mixture was stirred at room temperature 2.5 h then diluted with ethyl acetate (25 mL) and washed with H_2O (2 x 30 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. Purification of the two spots by reverse phase HPLC (C18 column) provided Compound 581 (58 mg, 62%) as a yellow powder after lyophilization: m.p. 136-148° (dec); ^1H NMR (300 MHz, CD_3OD) δ 7.47 (d, J =

8.7 Hz, 2H), 7.38 (d, J = 7.6 Hz, 2H), 7.2-7.3 (m, 2H), 7.0-7.1 (m, 3H), 6.8-6.9 (m, 2H), 6.71 (s, 2H), 6.59 (d, J = 8.8 Hz, 2H), 5.00 (dt, J = 3.2, 10 Hz, 1H), 4.03 (dt, J = 2.7, 9.2 Hz, 1H), 3.5-3.7 (m, 3H), 3.2-3.3 (m, 1H), 1.5-2.1 (m, 4H); IR (KBr) 3327, 1717, 1604, 1233 cm^{-1}; MS m/e calc'd for $C_{36}H_{34}N_3O_{11}$ (M^+ + 1): 684.2186, found 684.2256; Analysis calc'd for $C_{36}H_{33}O_{11}N_3 \circ 0.7\ H_2O$: C, 62.10; H, 4.98; N, 6.04; found: C, 61.86; H, 5.36; N, 6.44.

Trans-1-(4-hydroxybenzamido)-2-[4-(2-hydroxybenzoyl)-3,5-dihydroxybenzoyloxyl]cycloheptane (COMPOUND 582)

The catalyst $Pd(OH)_2$ on carbon (20%, moist, 9 mg) was added to a solution of *trans*-1-(4-benzyloxybenzamido)-2-[4-(2-benzyloxybenzoyl)-3,5-dibenzyloxybenzoyloxyl] cycloheptane (112 mg, 0.13 mmol) in methanol (3.9 mL) and ethyl acetate (1.3 mL). The mixture was stirred vigorously at room temperature under 1 atm H_2 contained in a balloon for 17 hours. The solid catalyst was removed by filtration through Florisil. The filtrate was evaporated and purified by flash chromatography (SiO_2 2:2:1/ethyl acetate: hexane: methylene chloride) to give a pale yellow powder (40 mg, 61%): mp 234-236°C; ^{1}H NMR (CD_3OD) δ 7.56 - 7.59 (m, 2H), 7.47 (t, J = 7.1 Hz, IH), 7.23 (d, J = 8.0 Hz, 1H), 7.00 (s, 2H), 6.96 (d, J = 8.2 Hz, 1H), 6.74 - 6.78 (m, 2H), 5.15 (tm, J = 9.3 Hz, 1H), 4.40 (tm, J = 9.3 Hz, 1H), 1.58 - 2.05 (m, 10H) IR (KBr) cm^{-1} 3392, 1700, 1678, 1626. Anal. calcd. for $C_{28}H_{27}O_8N$: C, 66.53; H, 5.38; N, 2.77. Found: C, 66.37; H, 5.56; N, 2.47.

Trans-1-(4-hydroxybenzamido)-2-[4-(2-hydroxycarbonylbenzoyl)-3,5-dihyroxybenzoyloxyl]cycloheptane (COMPOUND 583)

The catalyst $Pd(OH)_2$ on carbon (20%, moist, 17 mg) was added to a solution of *trans*-1-(4-benzyloxybenzamido)-2-[4-(2-benzyloxycarbonylbenzoyl)-3,5-dibenzyloxybenzoyloxyl) cycloheptane (220 mg, 0.24 mmol) in methanol (5mL) and ethyl acetate (12mL). The mixture was stirred vigorously at room temperature under 1 atm H_2 contained in a balloon for 16

hours. The solid catalyst was removed by filtration through Florisil. The filtrate was evaporated and purified by flash chromatography (SiO_2, diethyl ether followed by 5% methanol in diethyl ether) to give a yellow powder (87 mg, 68%): mp 190-193°C; ^1H NMR (CD_3OD) δ 7.97 (d, J = 7.5 Hz, 1H), 7.46 - 7.62 (m, 4H), 7.21 (d, J = 7.7 Hz, 1H), 6.86 (s, 2H), 6.72 - 6.77 (m, 2H), 5.16 (tm, J = 9.1 Hz, 1H), 4.34 (tm, J = 9.1 Hz, 1H), 1.56 - 2.02 (m, 10H) IR (KBr) cm^{-1} 3397, 1715, 1702, 1635. Anal. calcd. for $C_{28}H_{27}O_9N$: C, 65.29; H, 5.10; N, 2.63. Found: C, 65.18; H, 5.4; N, 2.29.

Anti-4-(3,5-dihydroxy-4-(3,4-dihydroxybenzoyl)benzoylamino)-hexahydro-3-(4-hydroxybenzoylamino)azepine, TFA salt, hydrate (1:1.1:1.5) (COMPOUND 584)

anti-4-Azidohexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine

A cooled (5°C) solution of *syn*-hexahydro-4-hydroxy-3-(4-phenylmethoxy)-benzoylamino-1-phenylmethylazepine (0.43 g, 1.0 mmol), dimethylaminopyridine (20 mg), and triethylamine (0.25 mL, 1.8 mmol) in anhydrous methylene chloride (4 mL) under nitrogen was treated dropwise with a solution of methanesulfonyl chloride (0.13 g, 1.13 mmol) in anhydrous methylene chloride (2 mL). The mixture was stirred on an ice bath for one hour, diluted with anhydrous dimethylsulfoxide (2.0 mL), and gently concentrated *in vacuo* at or near room temperature to remove methylene chloride (caution: remove all methylene chloride- it can give an explosive mixture with sodium azide and DMSO). Sodium azide (0.52 g, 8 mmol) was added, and the mixture was heated to 50 - 55°C for 4 hours, then cooled to room temperature. The solution was diluted with 0.5 N sodium hydroxide (10 mL) and extracted with ether (3x15 mL). The combined extracts were dried ($MgSO_4$) concentrated *in vacuo*, and flash chromatographed quickly on a silica gel column (eluted with 9:1 methylene chloride/acetone). The early high Rf chromophoric fractions were combined and concentrated to

afford *anti*-4-azidohexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.40 g, 88%, somewhat impure) as a viscous colorless oil, stored under nitrogen in the freezer.

Anti-4-(3,5-Bis(phenylmethoxy)-4-(3,4-bis(phenylmethoxy) benzoyl))-benzoylaminohexahydro-3-(4-phenylmethoxy) benzoylamino-1-phenylmethylazepine (COMPOUND 648)

A solution of *anti*-4-azidohexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethylazepine (0.39 g, 0.856 mmol) in 6:1:1 ethanol/acetic acid/water (12 mL) was treated with zinc powder (0.39 g, 6 mmol) and stirred at room temperature for one hour, then filtered and concentrated *in vacuo*. Meanwhile, a solution of 2,6,3',4'-tetrabenzyloxybenzophenone-4-carboxylic acid (0.65 g, 1.0 mmol) in anhydrous methylene chloride (3 mL) and N,N-dimethylformamide (0.1 mL) under nitrogen was treated dropwise with 2.0 N oxalyl chloride/methylene chloride (0.8 mL, 1.6 mmol), and after a short period of bubbling the solid had dissolved. The solution was stirred for one hour, concentrated *in vacuo*, and placed under high vacuum for 45 minutes (solid formed). The concentrated solid was dissolved in methylene chloride (8 mL) and added to the amine prepared by zinc reduction of the azide, and the mixture was treated with 1 N sodium hydroxide (5 mL), then stirred for two hours and separated. The aqueous solution was extracted with methylene chloride (2x25 mL) and the combined organic layer and extracts were washed with saturated sodium chloride, dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography on silica gel (eluted with 1:1 ethyl acetate/hexane) afforded anti-4-(3,5-bis(phenylmethoxy)-4-(3,4-bis(phenylmethoxy)benzoyl))-benzoylaminohexahydro-3-(4-phenylmethoxy)benzoylamino-1-phenylmethyl-azepine (0.44 g, 48%) as a white foam.

Anti-4-(3,5-Dihydroxy-4-(3,4- dihydroxybenzoyl)benzoylamino)-hexahydro-3-(4-hydroxybenzoylamin)azepine

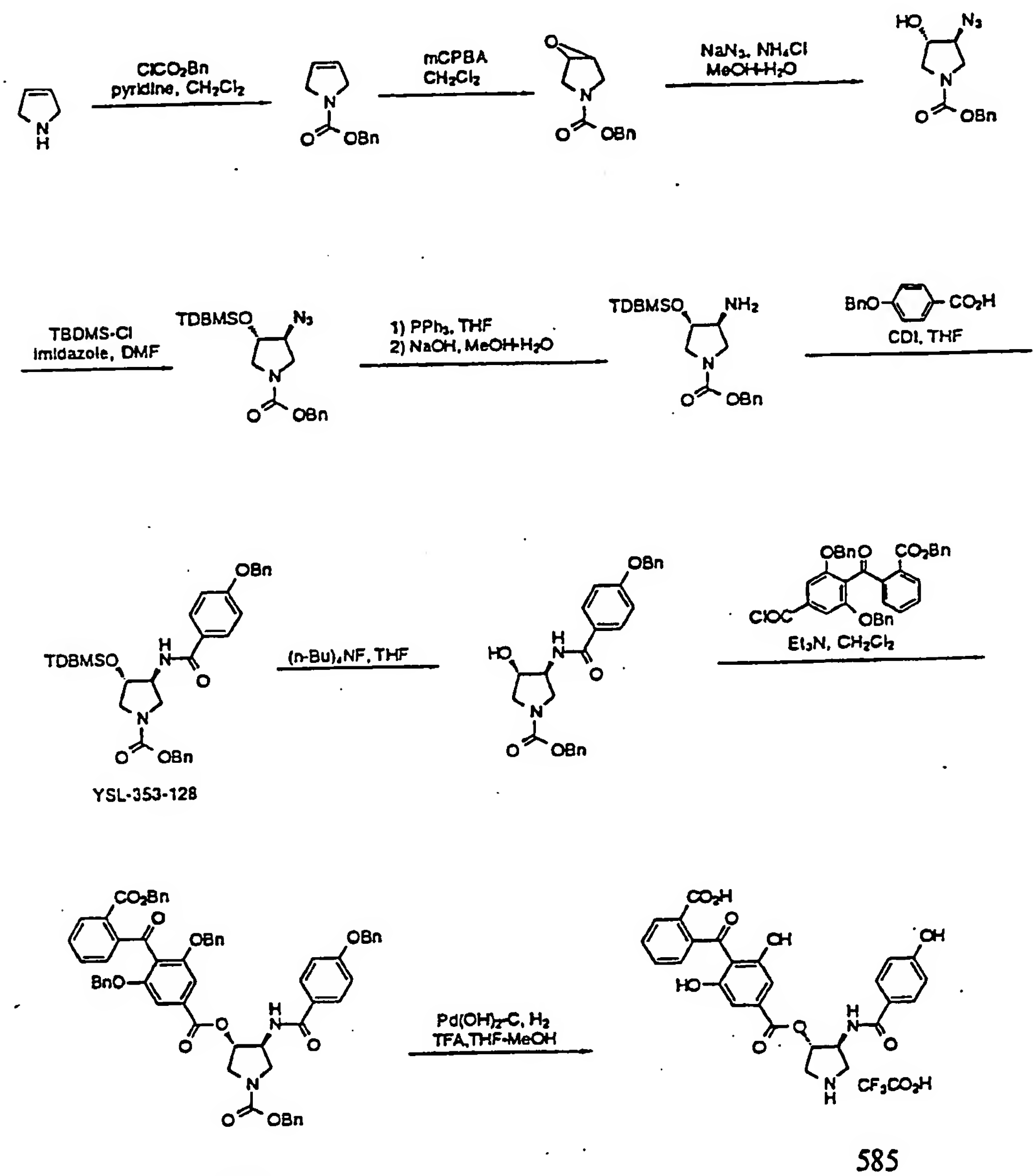
A solution of *anti*-4-(3,5-bis(phenylmethoxy)-4-(3,4-bis(phenylmethoxy)-benzoyl))benzoylaminohexahydro-3-(4-phenylmethoxy(benzoylamino-1-phenylmethylazepine (0.33 g, 0.31 mmol) in ethanol/ethyl acetate (1:1, 40 mL) was placed in a Parr bottle and treated (under nitrogen) with Pearlman's catalyst (Aldrich, 150 mg), then subjected to hydrogenation in a Parr apparatus for 18 h at 50 psi. The reaction mixture was carefully purged of hydrogen and the solution was filtered through celite (care taken not to let filter cake dry). The filtrate was concentrated *in vacuo* to afford crude material, which was taken up in acetonitriie containing a small amount of methanol and filtered (gravity). The filtrate was concentrated *in vacuo*, dissolved in warm isopropanol, filtered (gravity), reconcentrated to near dryness and diluted with ether. The precipitate was collected and dried *in vacuo* to afford anti-4-(3,5-dihydroxy-4-(3,4-dihydroxybenzoyl)benzoylamino)-hexahydro-3-(4-hydroxybenzoylamino)azepine (0.133 g, 82%) as a pale yellow powder.

Anti-4-(3,5-dihydroxy-4-(3,4-dihydroxybenzoyl)benzoylamino)-hexahydro-3-(4-hydroxybenzoylamino)azepine, TFA salt, hydrate (1:1.1:1.5) (COMPOUND 584)

Anti-4-(3,5-dihydroxy-4-(3,4-dihydroxybenzoyl)-benzoylamino)hexahydro-3-(4-hydroxybenzoylamino)azepine (70 mg, 0.134 mmol) was dissolved in methanol (2 mL), treated with a few drops of trifluoroacetic acid, and concentrated *in vacuo*. Preparative HPLC (C18 column, gradient elution by acetonitrile/water), followed by freeze-drying, afforded anti-4-(3,5-dihydroxy-4-(3,4-dihydroxybenzoyl)benzoylamino) hexahydro-3-(4-hydroxybenzoylamino)-azepine, TFA salt, hydrate (61 mg, 67%) as a voluminous white solid; mp 163-166°C. IR (KBr) 1612, 1650, 1674 cm^{-1}; ^1H NMR (d_6-DMSO) δ 10.09 (br s, 1H), 9.81 (br s, 1H), 9.68 (br s, 2H), 9.29 (br s, 1H), 8.88 (br s, 1H), 8.64 (br s, 1H), 8.34 (d, 1H, J = 8

Hz), 7.98 (d, 1H, J = 6 Hz), 7.74 (d, 2H, J = 9 Hz), 7.15 (d, 1H, J = 2 Hz), 7.04 (dd, 1H, J = 8 Hz, 2 Hz), 6.84 (d, 2H, J = 9 Hz), 6.76 (d, 1H, J = 8 Hz), 6.74 (s, 2H), 4.52 (m, 1H), 4.42 (m, 1H), 3.20 - 3.60 (m, 4H), 2.50 - 2.65 (m, 1H), 1.80 - 2.15 (m, 3H). Anal. Calcd. for $C_{27}H_{27}N_3O_8 \circ 1.1(C_2HO_2F_3) \circ 1.5(H_2O)$: C, 52.04; H, 4.65; N, 6.23. Found: C, 51.96; H, 4.69; N, 6.18.

Trans-3-(4-hydroxybenzamido)-4-[4-(2-hydroxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxyl]pyrrolidinium trifluoroacetate (COMPOUND 585)



649

585

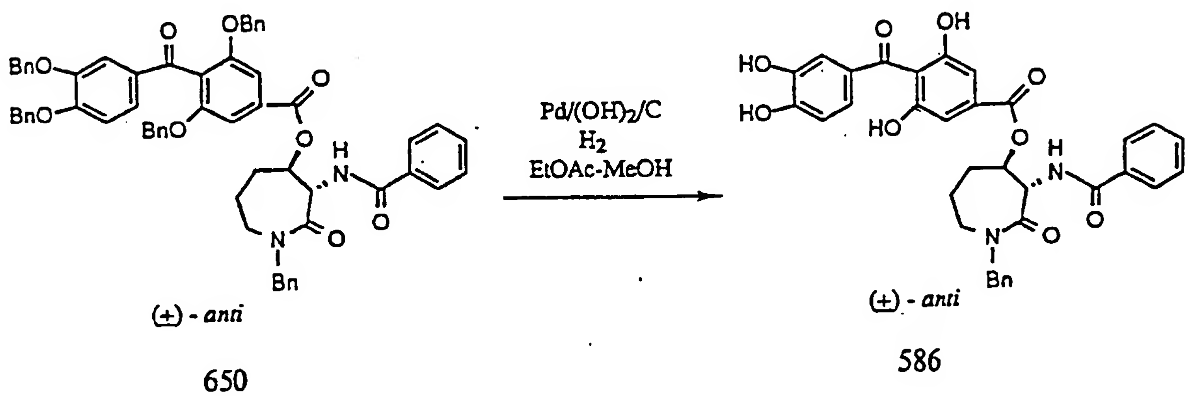
COMPOUND 649

To a solution of 4-(2-benzyloxycarbonylbenzoyl)-3,5-dibenzyloxybenzoic acid (314 mg, 0.55 mmol) in methylene chloride (1.6 mL) at 0°C was added oxalyl chloride (72 µL, 0.83 mmol), followed by 2 drops of N,N-dimethylformamide. The resultant mixture was stirred at 0°C for 1.5 h, evaporated, redissolved in methylene chloride (1 mL), and added to 3-(4-benzyloxybenzamido)-4-hydroxy-1-benzyloxycarbonyl pyrrolidine (220 mg, 0.5 mmol) and triethylamine (101 mg, 1 mmol) in methylene chloride (1.5 mL) at 0°C. The resultant solution was stirred 30 min at 0°C and 16 h at room temperature, diluted with methylene chloride (10 mL), washed with H_2O (3 x 5 mL), dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2, Et_2O : hexane = 1:1, then Et_2O : hexane : CH_2Cl_2 = 2:2:1) to give a colorless oil (301 mg, 55%).

COMPOUND 585

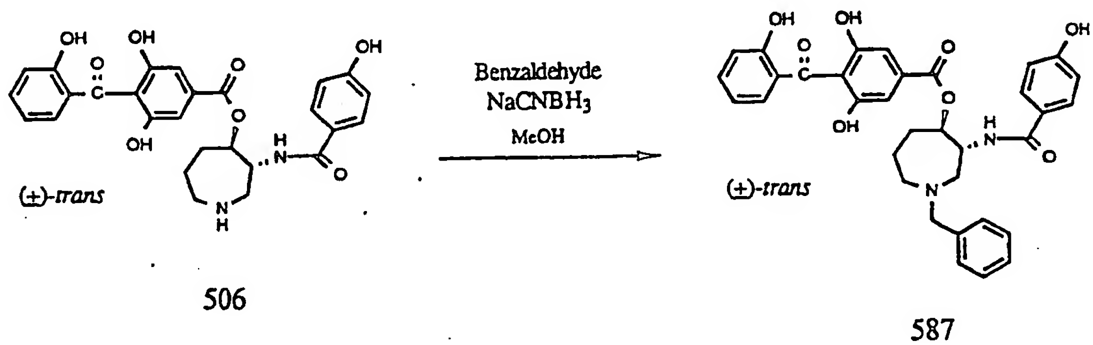
To a solution of 1-benzyloxycarbonyl-*trans*-3-(4-benzyloxybenzamido)-4-[4-(2-benzyloxycarbonylbenzoyl)-3,5-dibenzyloxybenzoyloxyl]pyrrolidine (Compound 649, 150 mg, 0.15 mmol) in THF (1.5 mL) were added moist $Pd(OH)_2$ on carbon (20 wt %, moisture content $\leq$ 50%; 21 mg, 0.015 mmol), MeOH (1.5 mL), and CF_3COOH (34 mg, 0.3 mmol), in that order. The resultant mixture was stirred vigorously at room temperature under 1 atm of H_2, contained in a balloon, for 20 h. The volatile material was removed by evaporation and the residue was taken up in MeOH (30 mL), filtered through Celite, and evaporated to give a yellow solid (83 mg, 83%). ^1H NMR (CD_3OD, 300 MHz): δ 7.77 (d, J = 7.9 Hz, 1H), 7.56 (tm, J= 8.7 Hz, 2H), 7.39 (t, J = 7.4 Hz, 1H), 7.28 (t, J = 7.4 Hz, 1H), 7.03 (d, J = 6.6 Hz, 1H), 6.76 (s, 2H), 5.42 (m, 1H), 4.51 (m, 1H), 3.77 (dd, J = 13.6, 5.2 Hz, 1H), 3.65 (dd, J = 12.6, 7.1 Hz, 1H), 3.44 (apparent dt, J = 12.5, 4.1 Hz, 2H). IR (KBr): cm^{-1} 3396, 2360, 2337. Anal. calcd. for $C_{28}H_{23}N_2O_{11}F_3$: C, 54.20; H, 3.74; N, 4.52 Found: C, 54.49; H, 3.92; N, 4.21.

(±)-*Trans*-N-Benzyl-3-benzamido-4-[3,5-dihydroxy-4-(3,4-dihydroxy)phenylcarbonyl]benz yloxycaprolactam (COMPOUND 586)



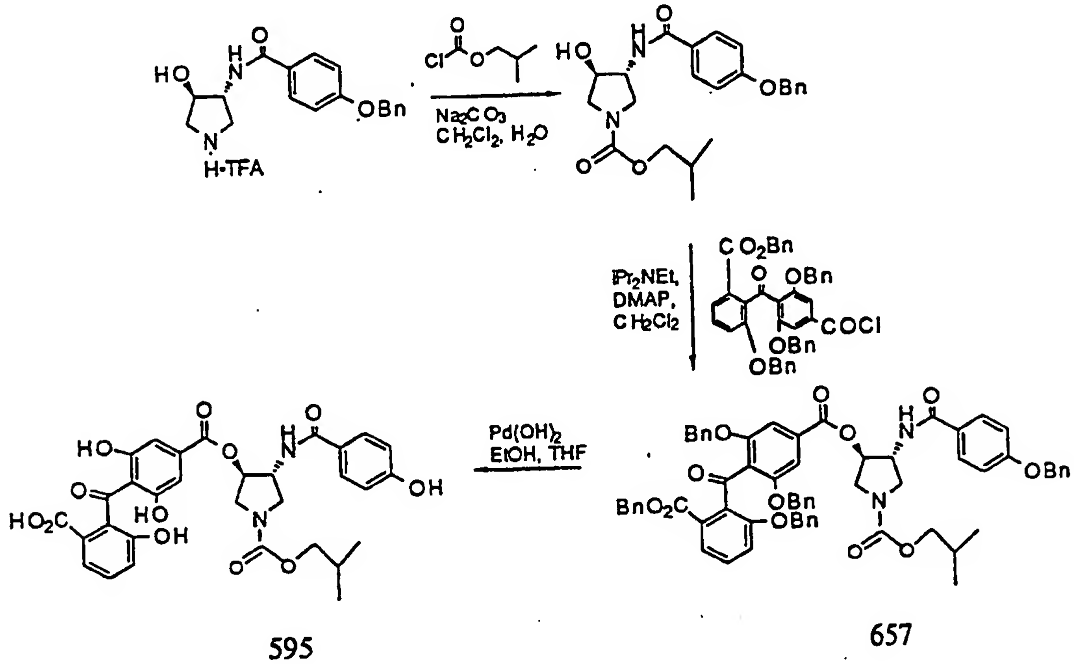
Hydrogenolysis of Compound 650 (280 mg, 0.288 mmol) was carried out in EtOAc-MeOH (1:1, 30 mL) in the presence of 20% $Pd(OH)_2/C$ (72 mg, 25% on weight basis) at 50 psi overnight. $Pd(OH)_2/C$ was filtered off through a pad of celite and raised with MeOH. The filtrate was subjected to flash column chromatograph using 5% MeOH in CH_2Cl_2. The yellow powder was obtained (96 mg, 55%): mp 152 - 155°C; ^{1}HNMR ($CDCl_3$) attached; IR (KBr) 3400, 1718, 1637, 1596, 1520. Anal. calcd. for $C_{34}H_{30}N_2O_9 \cdot 0.5H_2O$: C, 65.91; H, 5.04; N, 4.52. Found: C, 65.98; H, 5.14; N, 4.34.

(±)-*Trans*-3-(4-Hydroxy)benzamido-4-(3,5-dihydroxy-4-(2-hydroxy)phenylcarbonyl)benzoyl-N-Benzylazepine (COMPOUND 587)



The mixture of azepine (Compound 506, 50 mg, 0.099 mmol), cat. HOAc. and benzaldehyde (11.5 mg, 11.04 μl, 0.109 mmol) in MeOH (5 mL) was treated with $NaBH_3CN$ (7.8 mg, 0.118 mmol) at room temperature for 30 min. The reaction mixture was concentrated and purified on C_{18} - HPLC eluting with 1:1 (MeOH : H_2O containing 0.1% TFA. Yellow solid was obtained. ^{1}HNMR (CD_3CD) δ 7.40(d, J = 8.7 Hz, 2H, ArH), 7.27 (td, 1H, ArH), 7.06 (dd, 1H, ArH), 6.80 (s, 2H, ArH), 6.75 (d, 1H, ArH), 6.61 (d, 1H, ArH), 6.56 (d, J = 8.7 Hz, 2H, ArH), 5.01 (m, 1H, CH-4), 4.21 (m, 1H, CH-3), 2.92 - 2.64 (m, 4H, CH_2-2,7), 1.95 - 1.55 (m, 4H, CH_2-5,6).

(±)-*Trans*-4-[4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)-1-[(methylamino)carbonyl]pyrrolidine (COMPOUND 595)



(±)-*Trans*-4-Hydroxy-3-(4-benzyloxybenzamido)-1-[(isobutoxy)carbonyl]pyrrolidine

To a slurry of 3-(4-benzyloxybenzamido)-2-hydroxy pyrrolidine (150 mg, 0.352 mmol) in H_2O (8.8 mL) and CH_2Cl_2 (8.8 mL) were added anhydrous Na_2CO_3 (112 mg, 3.0 eq, 1.06 mmol) then isobutyl chloroformate (59 μL, 0.458 mmol, 1.3 eq), and the mixture stirred at room temperature 1.5 h. The solution was then poured into 5% HCl (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated to a white powder (142.5 mg, 98%): ^{1}H NMR (300 MHz, acetone-d_6) δ 7.86 (d, J = 8.8 Hz, 2H), 7.77 (bs, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.3-7.4 (m, 3H), 7.05 (d, J = 8.9 Hz, 2H), 5.17 (s, 2H), 4.75 (dd, J

= 7.3, 3.1 Hz, 1H), 4.3-4.4 (m, 2H), 3.6-3.9 (m, 4H), 3.4-3.5 (m, 1H), 3.3-3.4 (m, 1H), 1.85-2.0 (m, 1H), 0.91 (d, J = 6.9 Hz, 6H).

(±)-*Trans*-4-[4-(6-benzyloxy-2-(benzyloxycarbonyl)benzoyl]-3,5-dibenzyloxybenzoyloxy)-3-(4-benzyloxybenzamido)-1-[(isobutoxy)carbonyl]pyrrolidine (COMPOUND 657)

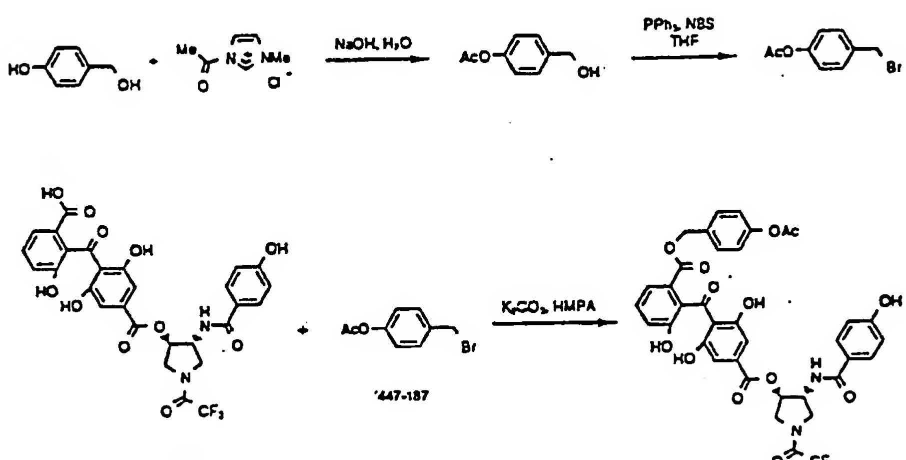
To a solution of the previous reaction product (142 mg, 0.345 mmol), diisopropylethylamine (60 μL, 1.0 eq., 0.345 mmol) and 4-dimethylaminopyridine (42 mg, 1.0 eq., 0.345 mmol) in CH_2Cl_2 (5.8 mL) under N_2 was added a solution of the acid chloride (0.368 mmol) in CH_2Cl_2 (2.9 mL). The reaction was allowed to stir 18 h. The cloudy reaction mixture was poured into 5% HCl (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated to a golden oil. Flash column chromatography (2:1 hexane:ethyl acetate) provided Compound 657 as an off white foam (252.1 mg, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.8 Hz, 2H), 7.3-7.45 (m, 5H), 7.2-7.3 (m, 19H), 6.95-7.2 (m, 8H), 6.84 (d, J = 7.2 Hz, 2H), 6.72 (bs, 1/2), 6.44 (bs, 1/2), 5.4-5.5 (m, 1H), 5.15 (s, 2H), 5.12 (s, 2H), 4.79 (s, 4H), 4.7 (m, 1H), 4.70 (s, 2H), 3.95-4.05 (bm, 2H), 3.85-3.95 (m, 2H), 3.5-3.7 (m, 1 1/2), 3.4-3.5 (m, 1/2), 1.9-2.0 (m, 1H), 0.96 (d, J = 6.7 Hz, 6H).

(±)-*Trans*-4-[4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)-1-[(methylamino)carbonyl]pyrrolidine (COMPOUND 595)

To a round bottom flask containing Compound 657 (252 mg, 0.235 mmol) were added $Pd(OH)_2$ (63 mg of a 20% powder) then THF (4.7 mL) and ethanol (4.7 mL). The flask was evacuated and filled with H_2 twice, then allowed to stir under H_2 (1 atm) for 17 h. The suspension was filtered, washed through with methanol (50 mL) and evaporated to a yellow solid. Purification by reverse phase HPLC (C18 column) provided Compound 595 as a yellow powder after lyophilization (117 mg, 80%): m.p. 170-185° (dec); IR (KBr)

3341, 3272, 1685, 1637, 1608, 1233, 767 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.52 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 7.1 Hz, 1H), 7.06 (dd, J = 8.0, 7.9 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 6.71 (s, 2H), 6.61 (d, J = 8.7 Hz, 2H), 5.23 (dd, J = 5.4, 2.8 Hz, 1H), 4.4-4.5 (m, 1H), 3.6-3.8 (m, 4H), 3.3-3.4 (m, 2H), 1.7-1.8 (m, 1H), 0.7-0.8 (m, 6H); MS m/e calc'd for $C_{31}H_{31}N_2O_{12}$: 623.1876, found 623.1884; Analysis calc'd for $C_{31}H_{30}N_2O_{12}$ • $2.2H_2O$: C, 56.15; H, 5.24; N, 4.22; found: C, 56.06; H, 5.10; N, 4.21.

1-Trifluoroacetyl-*trans*-3-(4-hydroxybenzamido)-4-{4-[2-acetoxybenzyloxycarbonyl)-6-hydroxybenzoyl]-3,5-dihydroxybenzoyloxyl}pyrrolidine (COMPOUND 596)



560

596

1-Methylimidazole (9.6 mL, 160 mmol) in Et_2O (120 mL) was added dropwise over 30 min. *via* an addition funnel to a stirred solution of acetyl chloride (8.5 mL, 120 mmol) at

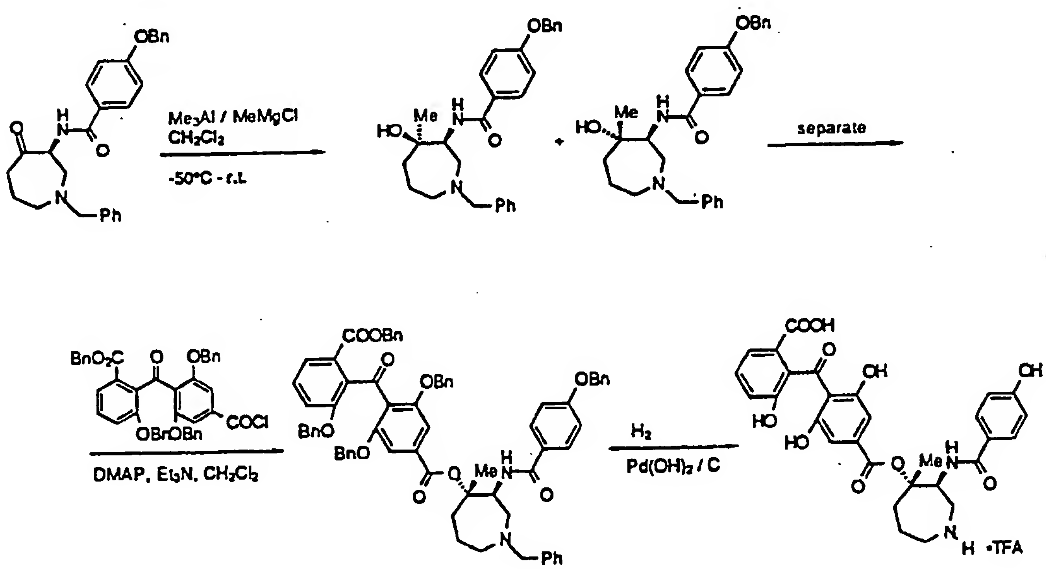
5°C. The resultant white precipitate was collected by filtration, washed with Et_2O (200 mL), and added in several portions to a solution of 4-hydroxybenzyl alcohol (4.96 g, 40 mmol) in 1N aq. NaOH (40 mL). The mixture was stirred at room temperature for 30 min., and then extracted with Et_2O (3 x 50 mL). The combined ether extracts were washed with H_2O (3 x 50 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2 followed by Et_2O: CH_2Cl_2 = 1:5) to give a pale yellow oil (2.06 g, 31%).

NBS (552 mg, 3.1 mmol) was added in several portions to the previous reaction product (498 mg, 3 mmol) and triphenylphosphine (813 mg, 3.1 mmol) in THF at 5°C. The resultant yellow solution was stirred at 5°C for 1 h, diluted with Et_2O (15 mL), washed with H_2O (3 x 10 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (SiO_2, Et_2O: hexane = 1:10) to give a white solid (430 mg, 63%) which is very unstable and should be used immediately otherwise stored under dry N_2.

COMPOUND 596

A mixture of Compound 560 (62 mg, 0.1 mmol), the previous reaction product (46 mg, 0.2 mmol), and K_2CO_3 (28 mg, 0.2 mmol) in HMPA (0.3 mL) was stirred at 50°C for 1.5 h, and the reaction was judged incomplete by TLC. Additional previous reaction product (23 mg, 0.1 mmol) was added and stirring was continued for 30 min. at 50°C. EtOAc (15 mL) was added and the resultant mixture was washed with H_2O (3 x 10 mL) and brine (10 mL); dried ($MgSO_4$), and evaporated. The residue was purified by preparative TLC (SiO_2, EtOAc: CH_2Cl_2 = 1:1) to give a yellow solid (40 mg, 52%). IR (KBr, cm^{-1}): 1727, 1693, 1636, 1607. FBMS: M/Z = 767 (M + 1).

Anti-4-[4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenz yloxy]-3-(4-hydroxybenzamido)-4-methylperhydroazepine trifluor acetic acid (COMPOUND 597)



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Anti-4-hydroxy-3-(4-benzyloxybenzamido)-4-methylperhydroazepine

To a 250 mL 3-neck round-bottom flask equipped with a thermometer under N_2 was added trimethylaluminum (18 mmol, 9.0 mL, 2M solution in toluene). This was cooled to 5°C in an ice/water bath and methylmagnesium chloride (13.5 mmol, 4.5 mL, 3M solution in THF) was added. This mixture was cooled to -50°C in a dry ice/acetone bath.

To a separate flask was added N-benzyl-3-(4-benzyloxybenzamido)-4-azepinone (1.07 mmol, 460 mg) and 30 mL anhydrous CH_2Cl_2. This was cooled to 0°C and added dropwise via cannula to the $(CH_3)_4AlMgCl$ solution. The cloudy reaction mixture was allowed to stir under N_2 and slowly warm

to room temperature where it became homogeneous. After 20 hours, acetone (4 mL) was added, the reaction was cooled in an ice/water bath and 5% $NaHCO_3$ (30 mL) was added slowly. The resulting emulsion was filtered through Celite, the layers separated and the aqueous layer extracted with CH_2Cl_2. The organic layers were dried and concentrated *in vacuo* to yield a mixture of diastereomeric products. Separation *via* flash column chromatography yielded the anti (112 mg, 24% yield) and syn (81 mg, 17% yield) products.

Anti-N-benzyl-4-[4-(2-benzyloxycarbonyl-6-benzyloxybenzoyl)-3,5-dibenzyloxy]-3-(4-benzyloxybenzamido)-4-methylazepine (COMPOUND 658)

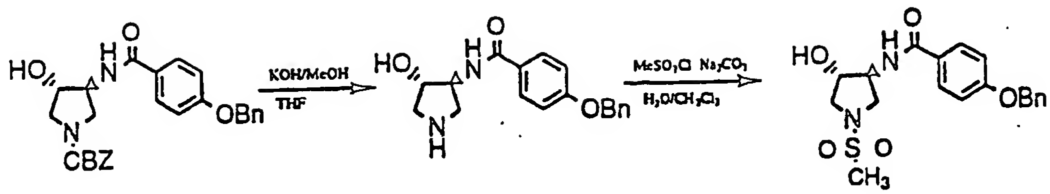
To a dry 25 mL round-bottom flask under N_2 was added 4-[4-(2-benzyloxy-6-benzyloxycarbonyl)benzoyl)-3,5-dibenzyloxybenzoic acid (0.37 mmol, 253 mg) and 4 mL anhydrous CH_2Cl_2. After cooling to 0°C oxalyl chloride (1.15 mmol, 0.1 mL) then DMF (2 drops) were added. This was allowed to stir for 1 hour while warming to room temperature. Monitoring by TLC (solvent system: 2:1 Hexanes: EtOAc) indicated complete formation of the acid chloride. The solvent was removed *in vacuo* to yield the acid chloride as an orange/brown oil.

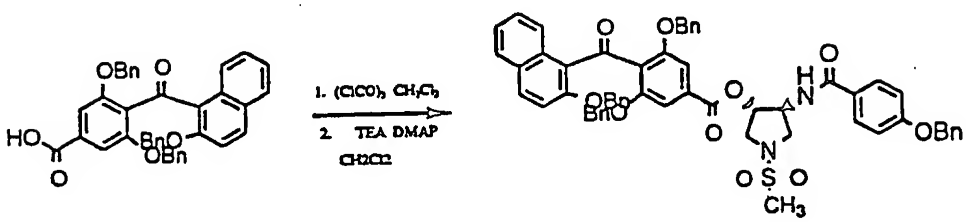
To a 50 mL round bottom flask under N_2 was added anti-4-hydroxy-3-(4-benzyloxybenzamido)-4-methylazepine (0.25 mmol, 109 mg) in 4 mL anhydrous CH_2Cl_2. This was followed by addition of DMAP (tip of spatula) and triethylamine (1.43 mmol, 0.2 mL). A solution of the acid chloride (generated above) in 4 mL CH_2Cl_2 was added and the mixture stirred for 16 hours at room temperature. The reaction was diluted with CH_2Cl_2, washed with 0.25 N NaOH (turned cloudy), dried and concentrated *in vacuo*. Purification *via* flash column (solvent: 10-50% acetone in CH_2Cl_2) yielded Compound 658 (131 mg, 47% yield) plus recovered anti-starting product (50 mg, 45%).

Anti-4-[4-(2-carb xy-6-hydr xybenz yl)-3,5-dihydroxybenz yloxy]-3-(4-hydroxybenzamido)-4-m thylazepine trifluoroacetic acid (COMPOUND 597)

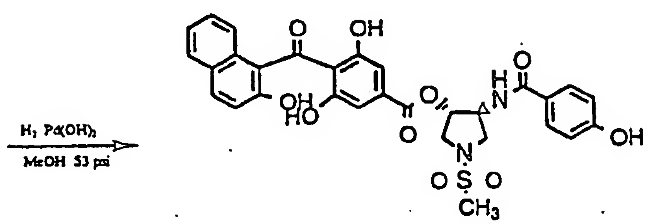
To a 100 mL 3-neck round-bottom flask under N_2 was added anti-N-benzyl-4-[4-(2-benzyloxycarbonyl-6-benzyloxybenzoyl)-3,5-dibenzyloxy]-3-(4-benzyloxybenzamido)-4-methylazepine (Compound 658, 0.12 mmol, 131 mg), 7.5 mL ethanol and 2 mL ethyl acetate. To this was added trifluoroacetic acid (0.40 mmol, 30 μL) then $Pd(OH)_2/C$ (80 mg). Immediately following the addition of $Pd(OH)_2$, H_2 was introduced at 1 atmosphere. The reaction stirred at room temperature under 1 atm H_2 for 24 hours. TLC indicated a complete reaction (solvent system: 8:1:1, butanol:water:acetic acid). The reaction was flushed with N_2, then filtered through Celite and concentrated. After purification by HPLC (21 mm C18 column, gradient %B = 0 to 50 over 60 min. where A = 0.1% TFA, 5% CH_3CN in water and B = CH_3CN, 15 mL/min., UV = 254nm) Compound 597 (38.5 mg, 47% yield) was isolated as a yellow powder. m.p. 176°C (dec.); IR (KBr) 3400 (br), 1677, 1635, 1607, 1504, 1425, 1369, 1243, 1199 cm^{-1}; ^1H NMR (DMSO-δ_6) δ 11.74 (s, 1H), 10.07 (s, 1H), 9.89 (s, 1H), 8.86 (m, 2H), 8.38 (d, 1H), 7.73 (d, 2H), 7.39 (d, 2H), 7.29 (t, 2H), 7.07 (m, 3H), 6.83 (d, 2H), 4.51 (t, 1H), 3.43 (under water peak, 1H), 3.14 (m, 3H), 2.72 (m, 1H), 1.99 (m, 1H), 1.77 (m, 2H), 1.57 (s, 3H); IRMS (M + 1) calcd for $C_{29}H_{29}N_2O_{10}$ 565.2, found 565.0. Anal. Calcd for $C_{29}H_{28}N_2O_{10}$ • $2H_2O$ • 1.1 TFA: C, 51.62; H, 4.60; N, 3.86. Found: C, 51.90; H, 4.25; N, 3.90.

Anti-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-1-naphthoyl)-3,5-dihydroxybenzyloxyl]-N-(methylsulfonyl)pyrrolidine (COMPOUND 599)





660

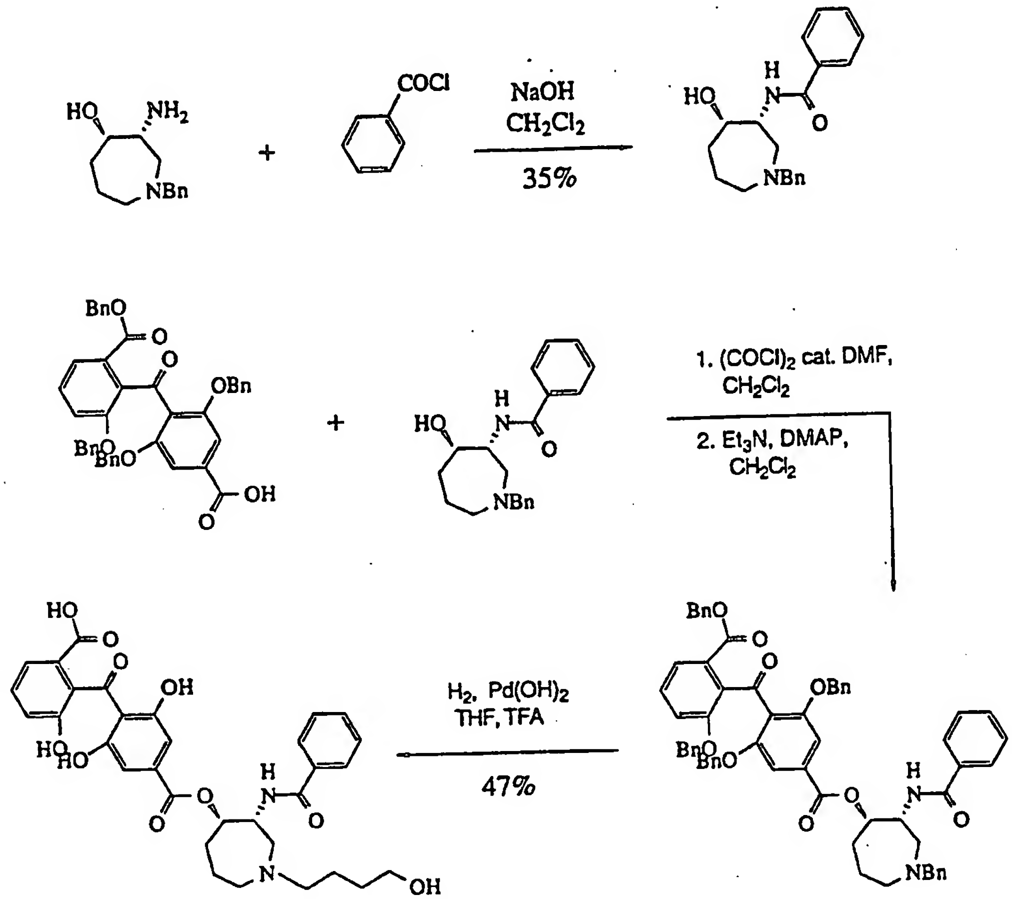


599

To a solution of Compound 660 (310 mg, 0.321 mmol) in methanol (40 mL) was added Pearlman's catalyst (150 mg, 50% by weight). The reaction mixture was shaken on a Parr apparatus under an atmosphere of hydrogen at a pressure of 53 psi. After six hours, the catalyst was filtered off through a pad of Celite® and the filtrate was concentrated. The crude material was purified by reverse-phase HPLC (50-100% B, A = 5% acetonitrile in water + 0.1% TFA, B = acetonitrile,

over one hour) to afford 101 mg of yellow powder (52%), which was triturated with toluene and dried to give Compound 599. mp = 158°-160°C. ^1H NMR δ (ppm) 8.55 (d, 1 H, J = 6.5 Hz), 7.85 (d, 1 H, J = 9 Hz), 7.75 (s, 1 H), 7.74 (d, 2 H, J = 8.5 Hz), 7.57-7.60 (m, 1 H), 7.27 (d, 1 H, J = 9 Hz), 7.26-7.27 (m, 1 H), 7.12 (d, 1 H, J = 9 Hz), 7.00 (s, 2 H), 6.83 (d, 2 H, J = 8.5 Hz), 5.50-5.51 (m, 1 H), 4.68-4.76 (m, 1 H), 3.85-3.98 (2H), 3.46-3.59 (m, 2 H), 2.97 (s, 3 H). IR (KBr disc) cm^{-1} 3399, 2929, 2362, 1719, 1685, 1636, 1607, 1560, 1542, 1508, 1459, 1426, 1363, 1326, 1277, 1225, 1177, 1148, 1105, 1053, 963, 910, 825, 754, 668. Anal. calcd. for $C_{30}H_{26}N_2O_{10}S \cdot 0.75\ H_2O$: C, 58.11; H, 4.47; N, 4.52; S, 5.17. Found: C, 58.12; H, 4.73; N, 4.52; S, 4.84. Mass spectral analysis (FAB): m/z (M + 1) = 607.

(+)-*Trans*-3-benzamido-4-[4-(2-carboxy-6-hydroxy)benzoyl-3,5-dihydroxy]benzoyloxy-N-(4-hydroxybutyl)hexahydroazepine trifluoroacetic acid salt (COMPOUND 661)



662 661

To a solution of benzoic acid (Aldrich, 183 mg, 1.49 mmol) in anhydrous CH_2Cl_2 (3 mL) was added cat. DMF and oxalyl chloride (2.0 M solution in CH_2Cl_2, 1.5 mL, 2.99 mmol) at room temperature. The mixture was stirred at room temperature for 2 hr. Solvents were removed and the acid chloride residue was taken into CH_2Cl_2 (5mL) after drying over the vacuum for 1hr. To a biphasic reaction mixture of azepine (300 mg, 1.36 mmol) in CH_2Cl_2 and 1N NaOH (6.8 mL, 6.8 mmol) was added a solution of benzoic acid chloride in anhydrous CH_2Cl_2 (10mL). The resulting mixture was vigorously stirred at room temperature for 30 min. The

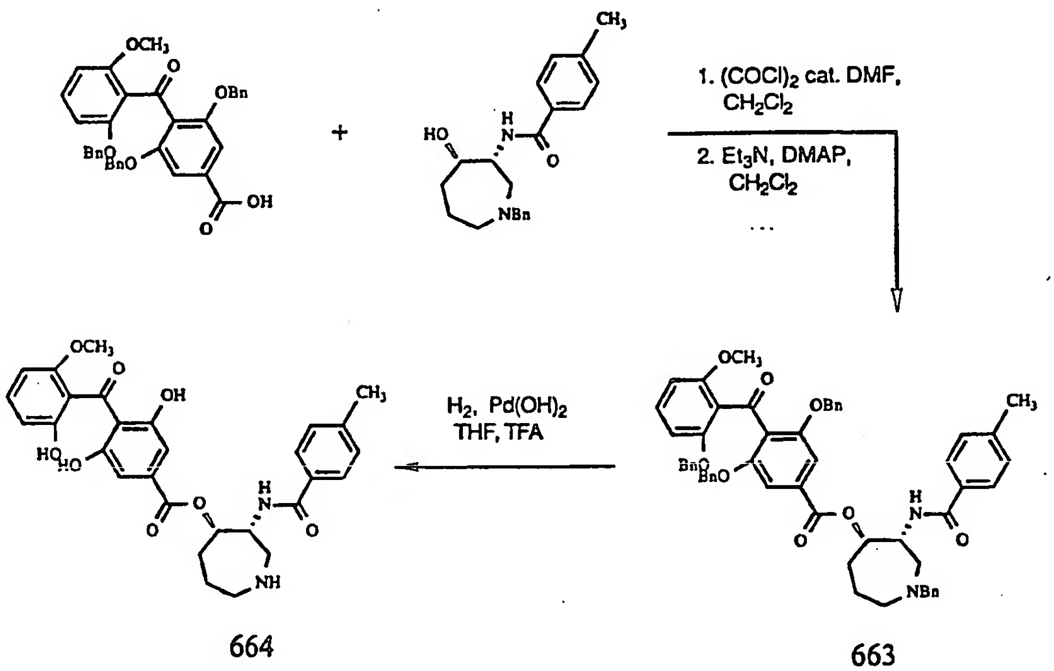
organic layer was separated and chromatographed using 2:1/EtOAc:Hexane to afford a wax-like solid (154mg, 35%).

To a solution of benzophenone acid (220 mg, 0.324 mmol) in CH_2Cl_2 (2 mL) was added cat. DMF and oxalyl chloride (2.0 M solution in CH_2Cl_2, 0.243 mL, 0.486 mmol) at room temperature. The mixture was stirred at room temperature for 2 hr. Solvents were removed and the acid chloride residue was taken into CH_2Cl_2 (5 mL) after drying over the vacuum for 1hr. A solution of amidoalcohol (105 mg, 0.324 mmol), Et_3N (163.9 mg, 226 μL, 1.62 mmol) and DMAP (7.9 mg, 0.065 mmol) in CH_2Cl_2 (5 mL) was treated with the freshly made acid chloride-CH_2Cl_2 solution (5 mL) at 5°C. The reaction mixture was allowed to stir at room temperature overnight and then chromatographed on silic gel with 1:2 / EtOAc: Hexane as an eluent to afford a light yellow film-like solid (Compound 661, 85 mg, 27%).

COMPOUND 662

Compound 661 (80 mg, 0.081 mmol) was dissolved in THF (10 mL) and treated with TFA (cat.) followed by 10% $Pd(OH)_2$ (55 mg, 60 mol%). The mixture was subject to hydrogenolysis at 50 psi for 40 hr. Solvents were concentrated after filtering through a pad of celite, and the residue was dissolved in DMF (0.25 mL) and loaded onto HPLC; conditions: A = 0.1%TFA and 5%CH_3CN in water, B = CH_3CN, 0-50%B over 60 min, 15 mL/min, 21x250 mm C18 column. Fractions (one/min) 29-30 were combined and concentrated to dryness to afford unexpected yellow solids (27.3 mg, 47%). N-Alkylation with THF in the presence of TFA occurred. m.p. 142-145 °C; 1H nmr (CD_3OD) δ 7.54 (d, J = 7.4 Hz, 2H, ArH), 7.37-7.19 (m, 4H, ArH), 7.05 (t, 1H, ArH), 6.80 (d, J = 8.3 Hz, 1H, ArH), 6.67 (s, 2H, ArH), 5.25 (m, 1H, CH-4), 4.24 (m, 1H, CH-3), 3.43 (m, 5H, NCH_2) 2.20-1.44 (m , 8H, CH_2); IR (KBr) cm^{-1} 3391, 1701, 1676, 1636, and 1604. Anal. Calcd. for $C_{34}H_{34}N_2O_{10} \cdot 1.9C_2HF_3O_2$: C, 52.23; H, 4.40; N, 3.40. Found: C, 52.08; H, 4.49; N, 3.48. LRFAB (M + 1): 607.

(±)-*Trans*-3-(4-Methylbenzamido)-4-[4-(2-methoxy-6-hydroxy)benzoyl-3,5-dihydroxy]benzoyloxyhexahydroazepine trifluoroacetice acid salt (COMPOUND 664)



COMPOUND 663

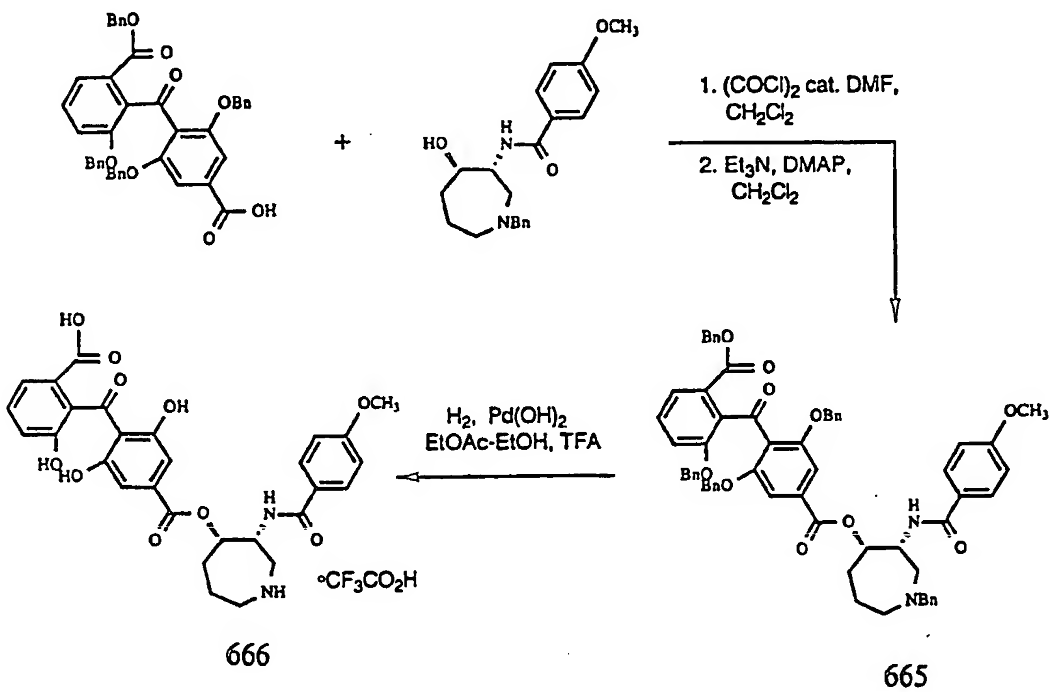
To a solution of benzophenone acid (150 mg, 0.261 mmol) in CH_2Cl_2 (3 mL) was added cat. DMF and oxalyl chloride (2.0 M solution in CH_2Cl_2, 0.25 mL, 0.5 mmol) at room temperature. The mixture was stirred at room temperature for 2 hr. Solvents were removed and the acid chloride residue was taken into CH_2Cl_2 (5 mL) after drying under vacuum for 1hr.

A solution of amidoalcohol (88 mg, 0.26 mmol), Et_3N (180 μL, 1.30 mmol) and DMAP (37 mg, 0.30 mmol) in CH_2Cl_2 (5 mL) was treated with the freshly made acid chloride-CH_2Cl_2 solution (5 mL) at 5°C. The reaction mixture was allowed to stir at room temperature overnight and then chromatographed on silic gel with 2:3 / EtOAc: Hexane as an eluent to afford white solids (70 mg, 30%). ^{1}H nmr ($CDCl_3$): attached.

COMPOUND 664

Compound 663 (60 mg, 0.067 mmol) was dissolved in THF (20 mL) and treated with TFA (cat.) followed by 10% $Pd(OH)_2$ (30 mg). The mixture was subjected to hydrogenolysis at 50 psi for 24 hr. Solvents were concentrated after filtering through a pad of celite, and the residue was dissolved in DMF (0.5 mL) and loaded onto HPLC; conditions: A = 0.1%TFA/5%CH_3CN/H_2O, B = 100%CH_3CN, 0-50%B over 60 min, 15 mL/min, 21x250 mm C18 column. Pure fractions were combined, concentrated, and lyophylized to a afford fluffy yellow solid (30 mg, 69%). m.p. 123-126 (dec) °C; 1Hnmr (CD_3OD) δ 7.64 (d, J = 8.2 Hz, 2H, ArH), 7.31 (t, 1H, ArH), 7.24 (d, J = 8.2 Hz, 2H, ArH), 6.95 (s, 2H, ArH), 6.50 (d, J = 8.2 Hz, 1H, ArH), 6.40 (d, J = 8.3 Hz, 1H, ArH), 5.41 (m, 1H, CH-4), 4.69 (m, 1H, CH-3), 3.48 (d, J = 5.2 Hz, 2H, NCH_2), 3.37 (s, 3H, CH_3), 2.30-2.00 (m, 4H, CH_2); IR (KBr) cm^{-1} 3449, 1676, and 1621. Anal. Calcd. for $C_{29}H_{30}N_2O_8 \cdot 1.0C_2HF_3O_2$: C, 53.68; H, 5.23; N, 4.04. Found: C, 53.34; H, 5.03; N, 4.35. LRFAB (M + 1):535.

(+)-*Trans*-3-(4-M thoxybenzamido)-4-[4-(2-carboxy-6-hydroxy benzoyl)-3,5-dihydroxybenzoyloxy]hexahydroazepine trifluoroacetic acid salt



COMPOUND 665

To a solution of benzophenone acid (235 mg, 0.346 mmol) in CH_2Cl_2 (3 mL) was added cat. DMF and oxalyl chloride (2.0 M solution in CH_2Cl_2, 0.433 mL, 0.865 mmol) at room temperature. The mixture was stirred at room temperature for 2 hr. Solvents were removed and the acid chloride residue was taken into CH_2Cl_2 (5mL) after drying under vacuum for 1 hr.

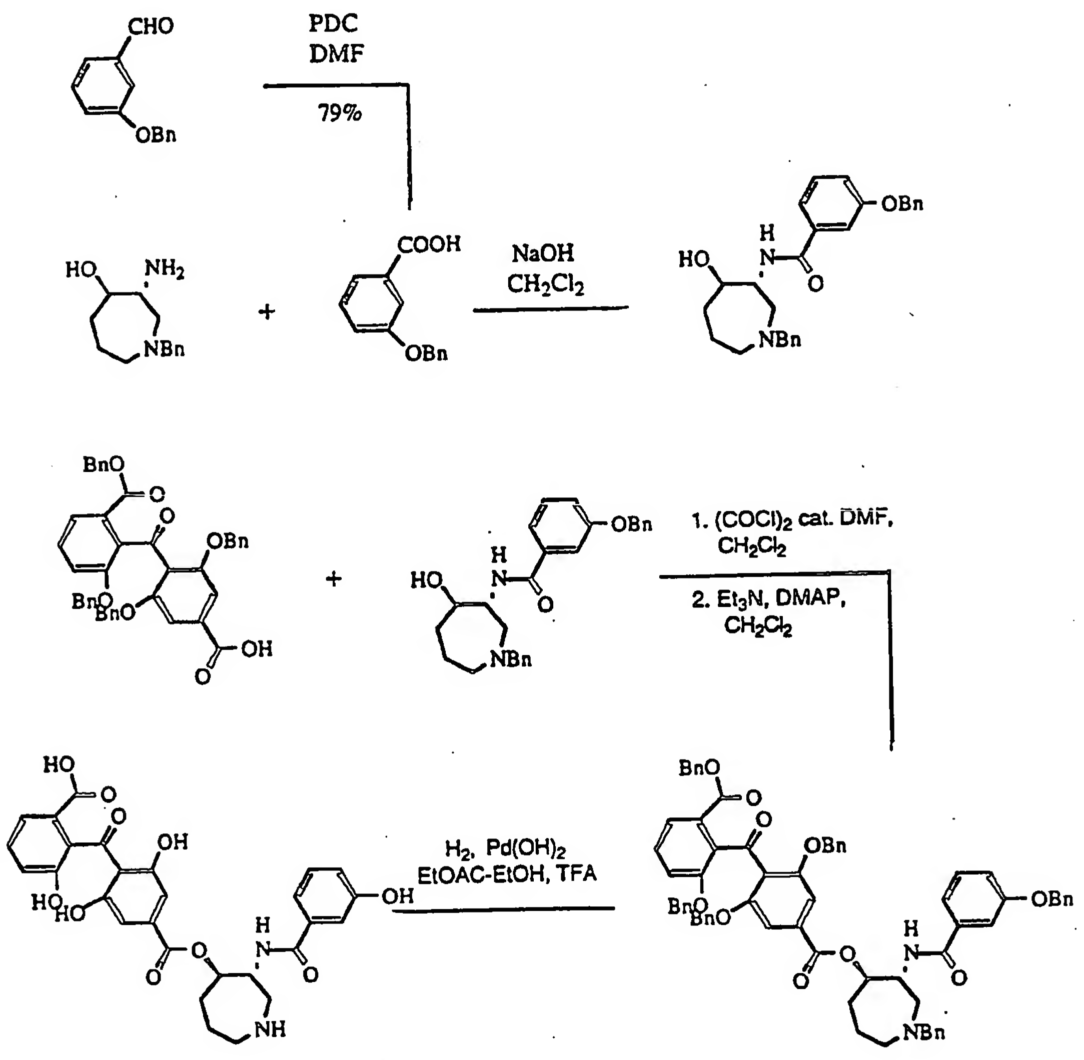
A solution of the amidoalcohol (122.63 mg, 0.346 mmol), Et_3N (175.06 mg, 241 μL, 1.73 mmol) and DMAP (42.27 mg, 0.346 mmol) in CH_2Cl_2 (5 mL) was treated with the freshly

made acid chloride-CH_2Cl_2 solution (5 mL) at 5°C. The reaction mixture was allowed to stir at room temperature overnight and then chromatographed on silica gel with 1:2 to 2:3 / EtOAc: hexane as an eluent to afford a white solid (170 mg, 48%).

COMPOUND 666

Compound 665 (165 mg, 0.163 mmol) was dissolved in EtOAc-EtOH (1:1, 20 mL) and treated with TFA (cat.) followed by 10% $Pd(OH)_2$ (100 mg, 58 mol%). The mixture was subject to hydrogenolysis at 50 psi for 20 hr. Solvents were concentrated after filtering through a pad of celite, and the residue was dissolved in DMF (0.75 mL) and loaded onto HPLC; conditions: A = 0.1%TFA/5%CH_3CN/H_2O, B = 100%CH_3CN, 0-50%B over 60 min, 25 mL/min, 41x300 mm C18 column. Fractions (one/min) 43-47 were combined, concentrated, and lyophylized to afford a fluffy yellow solid (99 mg, 90%). m.p. 178-180 (dec) °C; ^{1}Hnmr (CD_3OD) δ 7.74 (d, J = 8.7 Hz, 2H, ArH), 7.51 (d, J = 7.2 Hz, H, ArH), 7.29 (t, 1H, ArH), 7.04 (d, J = 8.3 Hz, 1H, ArH), 6.98 (d, J = 9.0 Hz, 2H, ArH), 6.90 (s, 2H, ArH), 5.45 (m, 1H, CH-4), 4.49 (m, 1H, CH-3), 3.84 (s, 3H, OCH_3), 3.50 (d, J = 5.8 Hz, 2H, NCH_2), 2.38-2.00 (m, 4H, CHz_2); IR (KBr) cm^{-1} 3447, 3371, 1699, 1681, 1650, 1634, 1610, and 1507. Anal. Calcd. for $C_{29}H_{28}N_2O_{10}$ • 2.59H_2O • 1.0$C_2HF_3O_2$: C, 51.46; H, 4.74; N, 3.87. Found: C, 51.13; H, 4.37; N, 3.82. LRFAB (M + 1) : 565.

(+)-*Trans*-3-(3-Hydroxybenzamido)-4-[4-(2-carb xy-6-hydroxy) b nzoyl-3,5-dihydroxy]benzoyloxyhexahydroazepine trifluoroacetic acid salt (COMPOUND 668)



668

667

The mixture of 3-benzyloxybenzaldehyde (Aldrich, 1.0 g, 4.7 mmol) and pyridinium dichromate (7.06 g, 18.4 mmol) in anhydrous DMF (7 mL) was stirred at room temperature

for 48h. The reaction mixture was then poured into water (50 mL) and extracted with CH_2Cl_2 (100 mL). The CH_2Cl_2 layer, which contained product as a sticky semi-solid, was washed with 1N HCl (2x80 mL) followed by extraction with 1N NaOH. The aqueous solution was then acidified by 4N HCl to pH 1-2 to precipitate a brown solid. Upon extractive workup of the solids with EtOAc (3x80 mL), the EtOAc layer was filtered through a pad of celite to get rid of most of chromate followed by flash chromatography using 0.15% HOAc in EtOAc as an eluent to afford a white solid (0.85 g, 79%).

To a solution of 3-benzyloxybenzoic acid (271.97 mg, 1.19 mmol) in anhydrous CH_2Cl_2 (3 mL) was added cat. DMF and oxalyl chloride (2.0 M solution in CH_2Cl_2, 1.56 mL, 3.12 mmol) at room temperature. The mixture was stirred at room temperature for 2 hr. Solvents were removed and the acid chloride residue was taken into CH_2Cl_2 (5 mL) after drying over the vacuum for 1hr. To a biphasic reaction mixture of azepine (250 mg, 1.13 mmol) in CH_2Cl_2 and 1N NaOH (6.0 mL, 6.0 mmol) was added a solution of 3-benzyloxybenzoic acid chloride in anhydrous CH_2Cl_2 (10 mL). The resulting mixture was vigorously stirred at room temperature for 3h. The organic layer was separated and chromatographed using 3:2/EtOAc: Hexane to a afford solid (221 mg, 43%).

COMPOUND 667

To a solution of benzophenone acid (300 mg, 0.442 mmol) in CH_2Cl_2 (2 mL) was added cat. DMF and oxalyl chloride (2.0 M solution in CH_2Cl_2, 0.55 mL, 1.11 mmol) at room temperature. The mixture was stirred at room temperature for 2 hr. Solvents were removed and the acid chloride residue was taken into CH_2Cl_2 (5 mL) after drying under vacuum for 1hr.

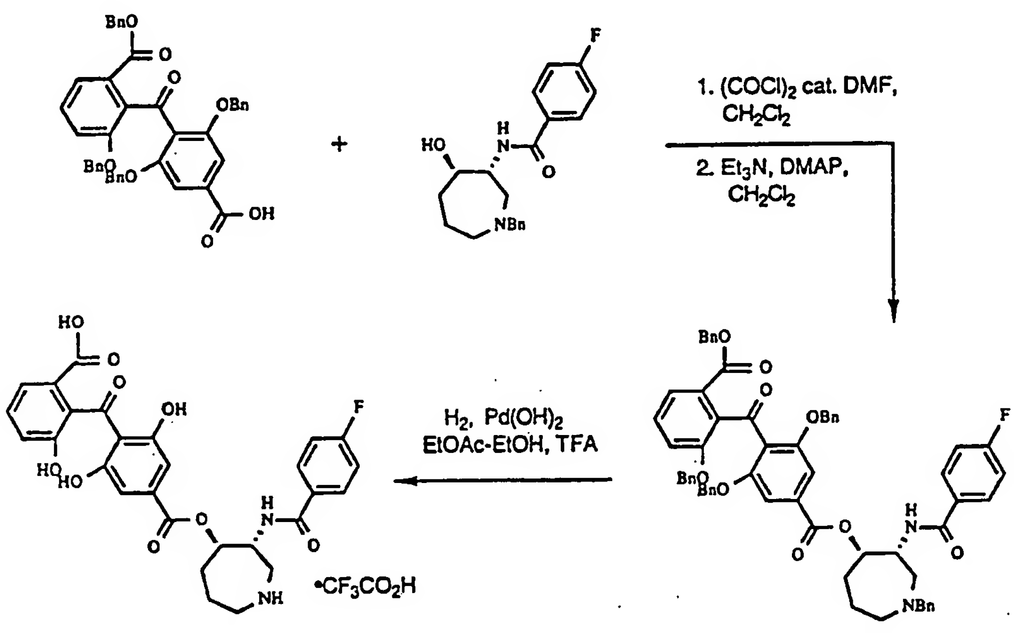
A solution of the amidoalcohol (190 mg, 0.442 mmol), Et_3N (223.6 mg, 308 μL, 2.21 mmol) and DMAP (54 mg, 0.442 mmol) in CH_2Cl_2 (5 mL) was treated with the freshly made acid chloride-CH_2Cl_2 solution (5 mL) at 5°C. The

reaction mixture was allowed to stir at room temperature overnight and then chromatographed on silic gel with 2:3 / EtOAc: hexane as an eluent to afford a foamy white solid (285 mg, 59%).

COMPOUND 668

Compound 667 (275 mg, 0.252 mmol) was dissolved in EtOAc-EtOH (3:2, 25 mL) and treated with TFA (cat.) followed by 10% $Pd(OH)_2$ (160 mg, 60 mol%). The mixture was subject to hydrogenolysis at 50 psi for 24 hr. Solvents were concentrated after filtering through a pad of celite, and the residue was dissolved in MeOH (1.75 mL) and loaded onto HPLC; conditions: A = 0.1%TFA/5%CH_3CN/H_2O, B = 100%CH_3CN, 0-50%B over 60 min, 25 mL/min, 41x300 mm C18 column. Pure fractions were combined, concentrated and partially lyophilized to afford pale yellow fluffy solids (125 mg, 75%). m.p. 184-186 (dec) °C; 1H nmr (CD_3OD) δ 7.49 (d, J = 8.0 Hz, 1H, ArH), 7.30-7.17 (m, 4H, ArH), 7.02 (d, J = 8.3 Hz, 1H, ArH), 6.94 (d, J = 7.87 Hz, 1Hm ArH), 6.90 (s, 2H, ArH), 5.45 (m, 1H, CH-4), 4.49 (m, 1H, CH-3), 3.50 (d, 2H, NCH_2), 2.30-2.0 (m, 4H, CH_2); IR (KBr) cm^{-1} 3443, 3433, 1700, 1680, 1650, and 1630. Anal. Calcd. for $C_{28}H_{26}N_2O_{10} \circ 2.5H_2O \circ 1.0C_2HF_3O_2$: C, 50.78; H, 4.54; N, 3.95. Found: C, 50.45; H, 4.36; N, 3.79. LRFAB (M + 1):551.

(+)-*Trans*-3-(4-Fluor benzamido)-4-[4-(2-carboxy-6-hydroxy)ben zoyl-3,5-dihydroxy]benzoyloxyhexahydroazepine trifluoroac tic acid salt (COMPOUND 670)



670

669

COMPOUND 669

To a solution of benzophenone acid (479 mg, 0.705 mmol) in CH_2Cl_2 (6 mL) was added cat. DMF and oxalyl chloride (2.0 M solution in CH_2Cl_2, 0.882 mL, 1.76 mmol) at room temperature. The mixture was kept for stirring at room temperature for 2 hr. Solvents were removed and the acid chloride residue was taken into CH_2Cl_2 (10 mL) after drying under vacuum for 1hr.

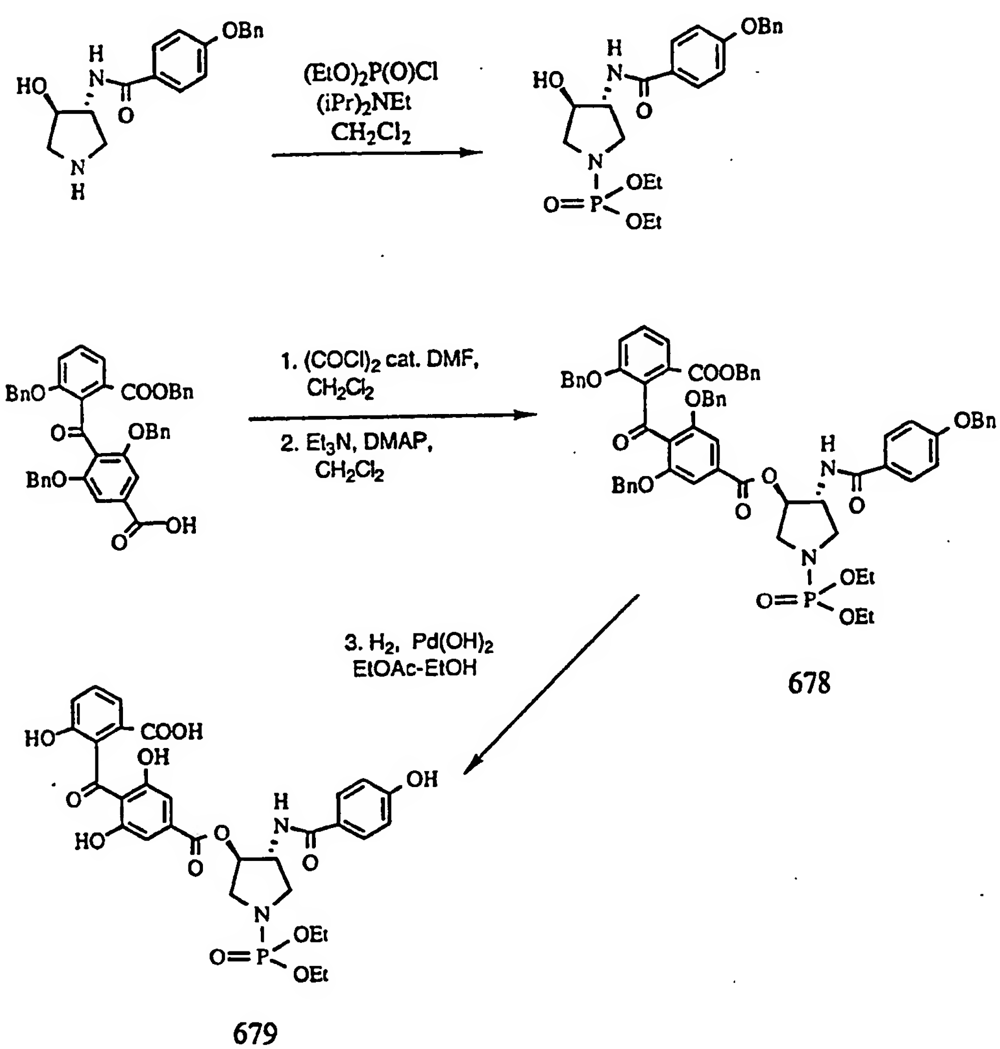
A solution of the amidoalcohol (210mg, 0.613 mmol), Et_3N (310 mg, 427 μL, 3.066 mmol) and DMAP (75 mg, 0.613 mmol) in CH_2Cl_2 (10 mL) was treated with the freshly made acid chloride-CH_2Cl_2 solution (10 mL) at 5°C. The reaction mixture was allowed to stir at room temperature overnight and

then chromatographed on silic gel with 2:3 / EtOAc: hexane as an eluent to afford a white solid (540 mg, 88%).

COMPOUND 670

Compound 669 (130 mg, 0.13 mmol) was dissolved in EtOAc-EtOH (3:1, 20 mL) and treated with TFA (cat.) followed by 10% $Pd(OH)_2$ (70 mg, 51 mol%). The mixture was subject to hydrogenolysis at 50 psi for 15 hr. Solvents were concentrated after filtering through a pad of celite, and the residue was dissolved in DMF (0.5mL) and loaded onto HPLC; conditions: A = 0.1%TFA/5%CH_3CN/H_2O, B = 100%CH_3CN, 0-50%B over 60 min, 15 mL/min, 21x250 mm C18 column. Fractions (one/min) 30-31 were combined and concentrated to afford yellow solids (54 mg, 62%). m.p. 175-178 (dec) °C; 1Hnmr (CD_3OD) δ 7.58 (t, 2H, ArH), 7.28 (d, J = 7.6 Hz, 1H, ArH), 7.06 (t, 1H, ArH), 6.94 (t, 1H, ArH), 6.80 (d, J = 8.1 Hz, 1H, ArH), 6.67 (s, 2H, ArH), 5.21 (m, 1H, CH-4), 4.28 (m, 1H, CH-3), 3.29 (d, J = 5.0 Hz, 2H, NCH_2), 2.20-1.70 (m , 4H, CH_2); IR (KBr) cm^{-1} 3367, 3307, 1704, 1634, and 1605. Anal. Calcd. for $C_{28}H_{25}FN_2O_9 \circ 1.75H_2O \circ 1.0C_2HF_3O_2$: C, 51.62; H, 4.26; N, 4.01. Found: C, 51.44; H, 3.90; N, 4.07. LRFAB (M + 1):553.

(+)-*Trans*-3-(4-Hydroxybenzamido)-4-[3,5-dihydroxy-4-(2-carboxy-6-hydroxybenzoylbenzoyloxy]-N-diethylphosphonato pyrrolidine (COMPOUND 679)



To a suspension of the amidoalcohol (300 mg, 0.96 mmol) in CH_2Cl_2 (30 mL) was added diisopropylethylamine (273 mg, 368 μl, 2.11 mmol), followed by diethyl chlorophosphate (182.2 mg, 153 μl, 1.06 mmol). The mixture was stirred at room temperature overnight before an extractive workup. The

crude product was purified by flash chromatography with 3% MeOH in CH_2Cl_2 as an eluent to afford a wax-like solid (421 mg, 84%).

COMPOUND 678

To a solution of benzophenone acid (272.4 mg, 0.4 mmol) in CH_2Cl_2 (5 mL) was added cat. DMF and oxalyl chloride (2.0 M solution in CH_2Cl_2, 0.5 mL, 1.0 mmol) at room temperature. The mixture was stirred at room temperature for 2 hr. Solvents were removed and the acid chloride residue was taken into CH_2Cl_2 (5 mL) after drying under vacuum for 1 hr.

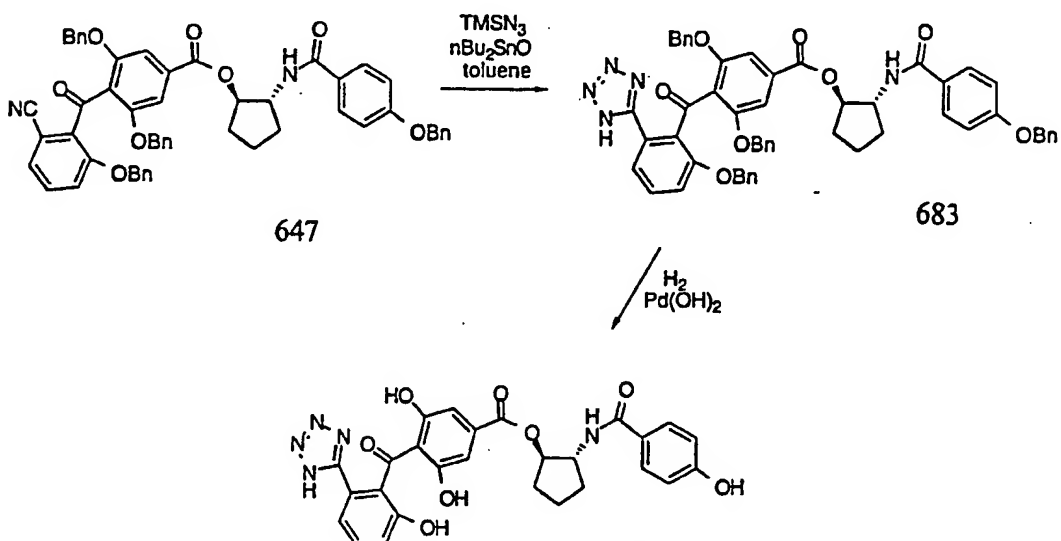
A solution of the amidoalcohol (150 mg, 0.334 mmol), Et_3N (170 mg, 233 μL, 1.67 mmol) and DMAP (40.8 mg, 0.334 mmol) in CH_2Cl_2 (5 mL) was treated with the freshly made acid chloride-CH_2Cl_2 solution (10 mL) at 5°C. The reaction mixture was allowed to stir at room temperature for overnight and then chromatographed on silic gel eluting with 3:1 / EtOAc: hexane. The product was obtained as a fluffy white solid (324 mg, 88%).

COMPOUND 679

Compound 678 (310 mg, 0.28 mmol) was dissolved in EtOAc-HOEt (2:1, 22.5 mL) and treated with 10% $Pd(OH)_2$ (134 mg, 45 mol%). The mixture was subject to hydrogenolysis at 50 psi for 20 hr. Solvents were concentrated after filtering through a pad of celite, and the residue was dissolved in DMF (0.4 mL) and loaded onto HPLC; conditions: A = 0.1%TFA/5%CH_3CN/H_2O, B = 100%CH_3CN, 0-50%B over 60 min, 25 mL/min, 41x350 mm C18 column. Fractions (one/min) 46-49 were combined and concentrated to dryness to afford 180 mg of yellow solids (98%). m.p. 188-190 (dec) °C; 1H nmr (CD_3OD) δ 7.73 (d, J = 8.9 Hz, 2H, ArH), 7.50 (d, J = 7.7 Hz, 1H, ArH), 7.27 (t, 1H, ArH), 7.02 (d, J = 7.1 Hz, 1H, ArH), 6.93 (s, 2H, ArH), 6.82 (d, J = 8.7 Hz, 2H, ArH), 5.43 (m, 1H, CH-4), 4.62 (m, 1H, CH-3), 4.07 (2q, 4H, $2OCH_2CH_3$) 3.77 (m , 2H,

NCH_2), 3.42 (m, 1H, NCH), 3,32 (m 1H, NCH), 1.27 (2t, 6H, $2OCH_2CH_3$); IR (KBr) cm^{-1} 3387, 3378, 1721, 1636, and 1607. Anal. Calcd. for $C_{30}H_{31}N_2PO_{13}$ • $0.5H_2O$: C, 53.98; H, 4.83; N, 4.20. Found: C, 53.78; H, 4.70; N, 3.93. LRFAB (M + 1) : 659.

(±)-*Trans*-2-[4-(6-hydroxy-2-tetrazolylbenzoyl)-3,5-dihydroxybenzoyloxy]-1-(4-hydroxybenzamido)cyclopentane (COMPOUND 684)



(±)-*Trans*-2-[4-(6-benzyloxy-2-tetrazolylbenzoyl)-3,5-dibenzyloxybenzoyloxy]-1-(2-benzyloxybenzamido)cyclopentane (COMPOUND 683)

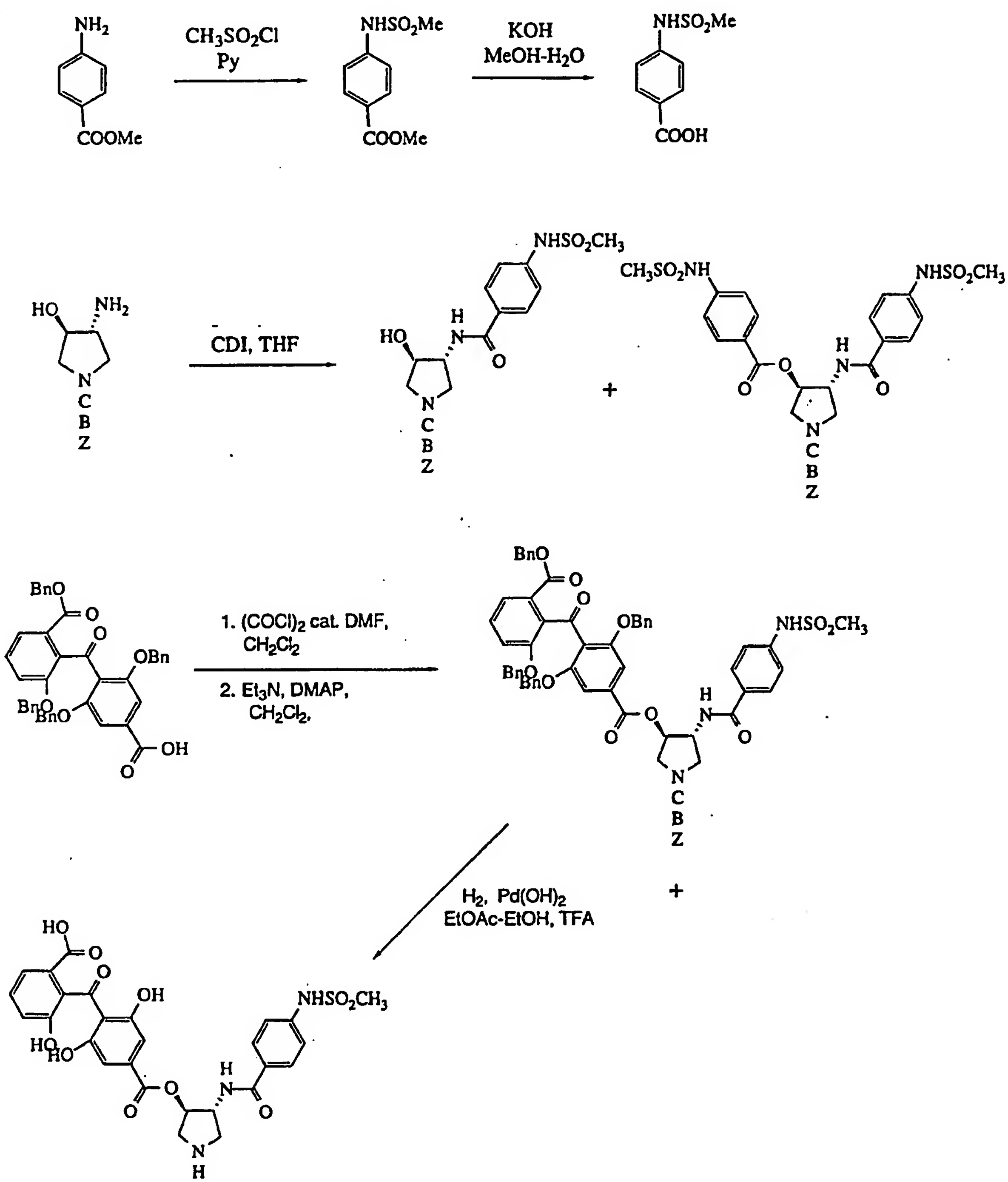
To a solution of Compound 647 (617 mg, 0.716 mmol) in toluene (3.6 mL) were added nBu_2SnO (178 mg, 0.716 mmol, 1.0 eq) then $TMSN_3$ (950 µL, 7.16 mmol, 10 eq). The mixture was heated at 70-80°C under N_2 20.5 h, at which time more toluene (1.0 mL) and $TMSN_3$ (950 µL) were added. After 48 h

total the solution was allowed to cool, poured into 5% HCl (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated. Flash column chromatography on silica gel (9:1 CH_2Cl_2: MeOH, two columns required for clean material) provided Compound 683 (253 mg, 39%) as a tan foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.7-7.8 (m, 3H), 7.45-7.5 (m, 1H), 7.3-7.4 (m, 6H), 7.1-7.2 (m, 5H), 7.0-7.1 (m, 4H), 6.9-7.0 (m, 7H), 6.83 (d, J = 6.9 Hz, 1H), 6.76 (d, J = 7.0 Hz, 2H), 5.25-5.35 (m, 1H), 5.07 (s, 1H), 5.06 (s, 2H), 4.70 (s, 3H), 4.68 (s, 2H), 4.5-4.6 (m, 1H), 2.3-2.45 (m, 1H), 2.2-2.3 (m, 1H), 1.8-1.95 (m, 2H), 1.5-1.75 (m, 2H).

(±)-*Trans*-2-[4-(6-hydroxy-2-tetrazolylbenzoyl)-3,5-dihydroxybenzoyloxy]-1-(4-hydroxybenzamido)cyclopentane (COMPOUND 684)

To a round bottom flask containing Compound 683 (132 mg, 0.146 mmol) and $Pd(OH)_2$ (33 mg of a 20% powder) were added THF (6.6 mL) and ethanol (6.6 mL). The flask was evacuated and filled with H_2 three times then stirred under H_2 (1 atm) for 15 h. The slurry was filtered through Celite, evaporated, and purified by reverse phase HPLC (C18 column). Compound 684 was obtained (53.0 mg, 67%) after lyophilization as a yellow powder: m.p. 154-164° (dec); ^{1}H NMR (300 MHz, CD_3OD) δ 7.47 (d, J = 8.7 Hz, 2H), 7.19 (dd, J = 7.9, 8.0 Hz, 1H), 7.07 (d, 8.8H), 6.82 (d, J = 8.2 Hz, 1H), 6.65 (s, 2H), 6.59 (d, 8.7H), 5.05. dt (10.4, J = 5.1 Hz, 1H), 4.2-4.3 (m, 1H), 1.95-2.1 (m, 2H), 1.6-1.7 (m, 2H), 1.4-1.6 (m, 2H); IR (KBr) 3383, 1704, 1607, 1246, 1197 cm^{-1}; MS m/e calc'd for $C_{27}H_{24}O_8N_5$ (M^+ + 2): 546.1624, found 546.1623; Analysis calc'd for $C_{27}H_{23}N_5O_8$ ∘ 0.5 TFA: C, 55.82; H, 3.93; N, 11.62; found: C, 55.63; H, 4.03; N, 11.82.

(+)-*Trans*-3-(4-Methanesulfonamidobenzamido)-4-[4-(2-carb xy-6-hydroxy)benzoyl-3,5-dihydroxy]benzoyl xypyrrolidine triflu roacetic acid salt



691

To a cold solution of methyl 4-aminobenzoate (2.0 g, 13.2 mmol) in pyridine (40 mL) was added methanesulfonyl chloride (1.81 g, 1.22 mL, 15.8 mmol). The mixture was allowed to stir at room temperature overnight. Pyridine was removed *in vacuo*, and the residue was taken into EtOAc (100mL) and washed with brine containing 0.1 N HCl (3x 60mL). A light purple solid was obtained upon drying over Na_2SO_4 and concentration (2.8 g, quantitative yield).

The mixture of methyl ester (2.8 g, 12.2 mmol) and KOH (10.2 g, 183.3 mmol) in MeOH-H_2O (4:1,100 mL) was stirred at room temperature for 24 h. Methanol was removed *in vacuo* and the aqueous was diluted with water and acidified by 4N HCl after being extracted with EtOAc (2x60mL). Solids which precipitated from the aqueous phase was collected (beige, 2.34g, 89%). IR (KBr) cm^{-1} 3276, 1681, 1607, 1319, and 1150. Anal. Calcd. for $C_8H^9NO^4S$: C, 44.64; H, 4.21; N, 6.51; S, 14.90. Found: C, 44.40; H, 4.16; N, 6.34; S, 15.20.

To a solution of acid (219 mg, 1.02 mmol) in anhydrous THF (5mL) was added CDI (206 mg, 1.27 mmol). The resulting mixture was stirred at room temperature for 2 h, to which a solution of N-CBZ-3-amino-4-hydroxypyrrolidine (222 mg, 0.846 mmol) in THF (3 mL) was added. After being stirred at room temperature overnight, the reaction mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, and chromatographed on silica gel with 4:1 / EtOAC: hexane + 2%MeOH as an eluent. 139 mg of the desired product and 134 mg of the diacyl product were obtained. Saponification of the diacyl product in MeOH-H_2O (1:1, 4 mL) using K_2CO_3 (393 mg, 2.85 mmol) afforded additional 71 mg of the desired product (total 210 mg, 57%).

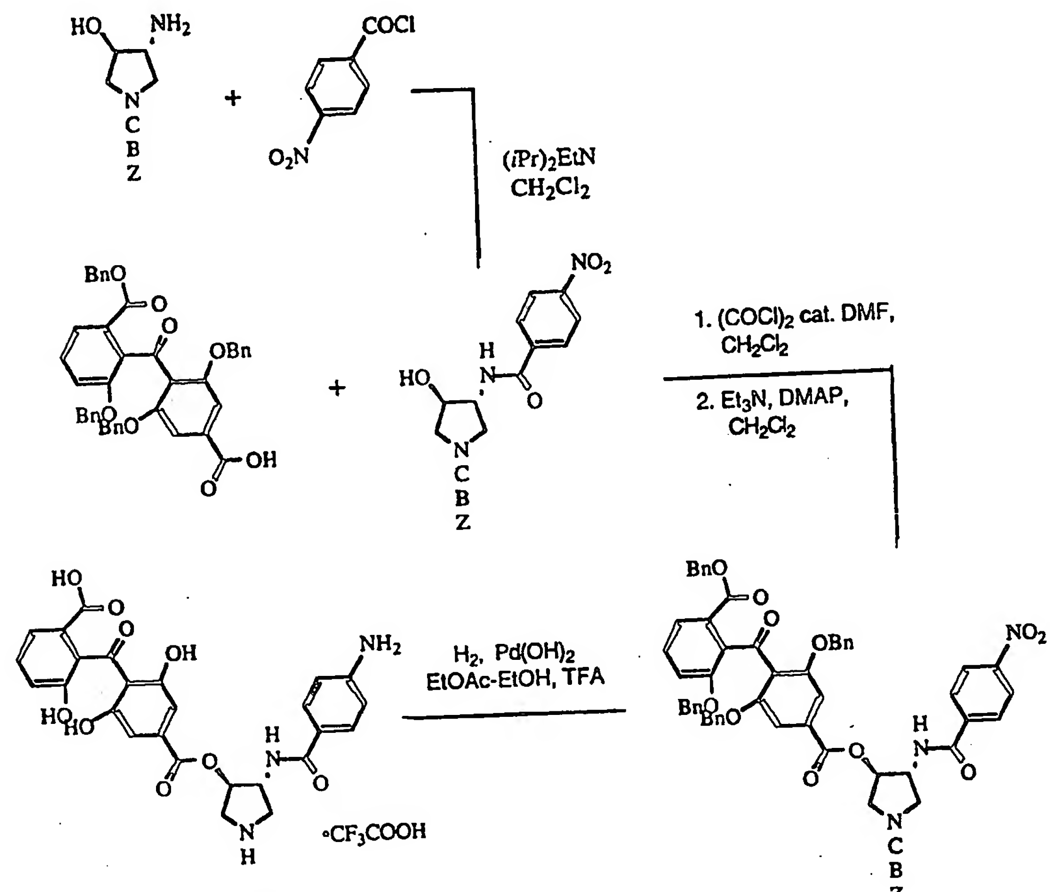
To a solution of benzophenone acid (252 mg, 0.37 mmol) in CH_2Cl_2 (3mL) was added cat. DMF and oxalyl chloride (2.0 M solution in CH_2Cl_2, 0.463mL, 0.927mmol) at room temperature. The mixture was stirred at room temperature for 2 hr. Solvents were removed and the acid chloride residue was taken into CH_2Cl_2 (5mL) after drying under vacuum for 1hr.

A solution of the amidoalcohol (140 mg, 0.322 mmol), Et_3N (163.4 mg, 225 μL, 1.61 mmol) and DMAP (40 mg, 0.322 mmol) in CH_2Cl_2 (5 mL) was treated with the freshly made acid chloride-CH_2Cl_2 solution (10 mL) at 5°C. The reaction mixture was allowed to stir at room temperature overnight and then chromatographed on silica gel eluting with 1:1 / EtOAc: Hexane + 1% MeOH. The product was obtained as a fluffy white solid (114 mg, 32%).

COMPOUND 691

The previous reaction product (100 mg, 0.091 mmol) was dissolved in EtOAc-HOEt (2:1, 15 mL) and treated with TFA (cat.) followed by 10% $Pd(OH)_2$ (58 mg, 60 mol %). The mixture was subject to hydrogenolysis at 50 psi for 15 hr. Solvents were concentrated after filtering through a pad of celite, and the residue was dissolved in DMF (0.4 mL) and loaded onto HPLC; conditions: A = 0.1%TFA/5%CH_3CN/H_2O, B = 100%CH_3CN, 0-50%B over 60 min, 25 mL/min, 41x350 mm C18 column. Fractions (one/min) 39-42 were combined and concentrated to dryness to afford 58 mg of a yellow solid (89%). m.p. 182-184 (dec)°C; 1H nmr (CD_3OD) δ 7.87 (d, J = 8.7 Hz, 2H, ArH), 7.50 (d, 1H, ArH), 7.31 (d, J = 8.3 Hz, 2H, ArH), 7.29 (t, 1H, ArH), 7.03 (d, J = 8.3 Hz, 1H, ArH), 6.70 (s, 2H, ArH), 5.64 (m, 1H, CH-4), 4.67 (m, 1H, CH-3), 4.00 and 3.87 (dd and dd, 2H, NCH_2) 3.64 (m, 2H, NCH_2), 3.04 (s, 3H, $NHSO_2CH_3$); IR (KBr) cm^{-1} 3371, 3210, 3086, 1721, 1673, 1609, 1199, and 1149. Anal. Calcd. for $C_{27}H_{25}N_3O_{11}S \cdot 1.7C_2HF_3O_2$: C, 46.02; H, 3.39; N, 5.30; S, 4.04. Found: C, 45.85; H, 3.48; N, 5.65; S, 4.03. LRFAB (M + 1):600.

(±)-*Trans*-3-(4-Aminobenzamido)-4-[4-(2-carboxy-6-hydroxy)benzoyl-3,5-dihydroxy]benzoyloxypyrrolidine triflu roacetic acid salt (COMPOUND 692)



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To a cold solution/suspension of N-CBZ-3-amino-4-hydroxypyrrolidine (220mg, 0.846mmol) and $(iPr)_2EtN$ (240mg, 324μL, 1.86mmol) in anhydrous CH_2Cl_2 (10mL) was added a solution of 4-nitrobenzoyl chloride (188.4mg, 1.02mmol) in CH_2Cl_2 (3mL) *via* a syringe. After stirring at room temperature overnight the reaction mixture was diluted with EtOAc, washed with brine, and chromatographed with 4:1 /

EtOAc / Hexane as an eluent to afford a white solid (367g, 93%).

To a solution of benzophenone acid (450 mg, 0.66 mmol) in CH_2Cl_2 (5 mL) was added cat. DMF and oxalyl chloride (2.0 M solution in CH_2Cl_2, 0.829 mL, 1.66 mmol) at room temperature. The mixture was stirred at room temperature for 2 hr. Solvents were removed and the acid chloride residue was taken into CH_2Cl_2 (10 mL) after drying under vacuum for 1hr.

A solution/suspension of the amidoalcohol (200 mg, 0.519 mmol), Et_3N (292 mg, 402 μL, 2.88 mmol) and DMAP (70.4 mg, 0.577 mmol) in CH_2Cl_2 (10 mL) was treated with the freshly made acid chloride-CH_2Cl_2 solution (10 mL) at 5°C. The reaction mixture was allowed to stir at room temperature for 3 h and then chromatographed on silica gel eluting with 3:2 / EtOAc: Hexane. The product was obtained as white solids (524 mg, 97%).

COMPOUND 692

The previous reaction product (220 mg, 0.21 mmol) was dissolved in EtOAc-HOEt (1:1, 15 mL) and treated with TFA (cat.) followed by 10% $Pd(OH)_2$ (269mg, 120 mol %). The mixture was subject to hydrogenolysis at 50 psi for 48 hr. Solvents were concentrated after filtering through a pad of celite, and the residue was dissolved in DMF (0.5 mL) and loaded onto HPLC; conditions: A = 0.1%TFA/5%CH_3CN/H_2O, B = 100%/CH_3CN, 0-50%B over 60 min, 25 mL/min, 41x300 mm C18 column. Fractions (one/min) 33-35 were combined, concentrated, and repurified by another HPLC. Condition: 30% MeOH for 20 min then increase to 100% MeOH over 15 min, 3 ml/min, 10 x 250mm C8 column. Fractions (one/min) 13-15 were combined and concentrated to afford a yellow solid (8mg, 6%). m.p.>184 (dec)°C; 1H nmr (CD_3OD) attached. IR (KBr) cm^{-1} 3376, 3232, 3077, 1725, 1677, 1631, and 1605. Anal. Calcd. for $C_{26}H_{23}N_3O_8 \cdot 1.0C_2HF_3O_2$: C, 52.92; H, 3.81; N, 6.61 Found: C, 52.81; H, 4.19; N, 6.48. LRFAB (M + 1): 522.

4-R°-(4-(3-Carboxy-4-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy)-3-R°-(4-hydroxybenzamido)azepine trifluoroacetic acid mono hydrate (COMPOUND 694)

Benzyl-2-benzyloxy-5-formylbenzoate

Anhydrous K_2CO_3 (0.900 g, 6.47 mmol) and benzyl bromide (846 µL, 7.11 mmol) were added to a stirred solution of 5-formyl salicylic acid (0.537 g, 3.23 mmol) in anhydrous N,N-dimethylformamide (32 mL) at room temperature under N_2. The resulting mixture stirred at room temperature for 16 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The oily residue was partitioned between EtOAc (150 mL) and water (100 mL). The organic portion was separated and washed with water (2 x 100 mL) and brine (75 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to afford an off-white solid which was recrystallized from EtOAc/hexanes to give benzyl-2-benzyloxy-5-formylbenzoate (0.819 g, 73%). m.p. 97-98°C.

t-Butyl-4-(3-benzyloxycarbonyl-4-benzyloxyhydroxymethyl)-3,5-dibenzyloxybenzoate

BuLi (972 µL, 2.1 M) in hexanes was added dropwise to a stirred solution of *t*-butyl-4-bromo-3,5-dibenzyloxybenzoate (0.871 g, 1.86 mmoL) in anhydrous THF at -80°C under N_2. The resulting dark purple solution stirred at -80°C for 15 m then a solution of benzyl-2-benzyloxy-5-formylbenzoate (0.634 g, 1.86 mmoL) in anhydrous THF (3 mL) was added dropwise at -80°C. The resulting solution was allowed to warm to room temperature as it stirred for 16 h. The solution was then partitioned between 0.1N HCl (50 mL) and EtOAc (100 mL). The organic portion was separated and washed with brine (75 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Subsequent chromatography on silica gel eluting with 7-10% EtOAc/Hex afforded *t*-Butyl-4-(3-benzyloxycarbonyl-4-benzyloxyhydroxymethyl)-3,5-dibenzyloxybenzoate (0.699 g, 51%) as a white foam. IR (KBr, cm^{-1}) 3539, 2975, 1709, 1250,

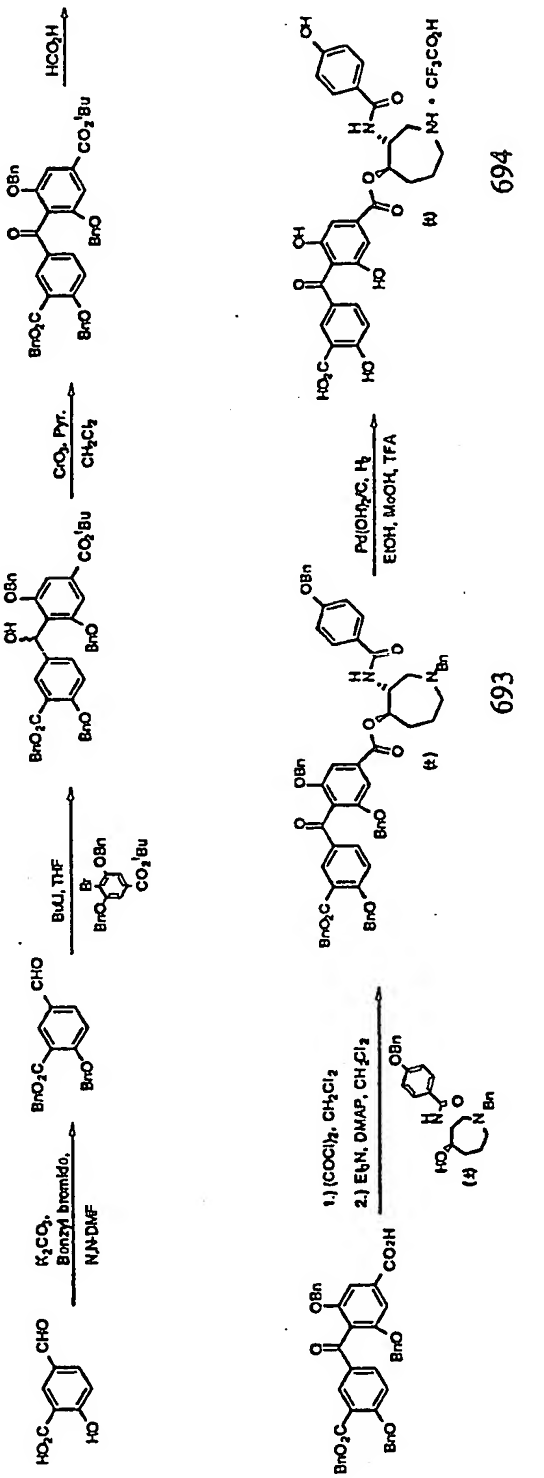
1096, 696. Anal. Calcd. for $C_{47}H_{44}O_8$: C, 76.61; H, 6.02. Found: C, 76.76; H, 6.13.

t-Butyl-4-(3-benzyloxycarbonyl-4-benzyloxybenzoyl)-3,5-dibenzyloxybenzoate

CrO_3 (2.75 g, 27.5 mmoL) was added in portions to a stirred solution of anhydrous pyridine (4.45 mL, 55.0 mmoL) in CH_2Cl_2 (100 mL) at room temperature under N_2. The resulting dark red mixture was stirred for 20 minutes. A solution of *t*-Butyl-4-(3-benzyloxycarbonyl-4-benzyloxyhydroxymethyl)-3,5-dibenzyloxybenzoate (3.38 g, 4.58 mmoL) in CH_2Cl_2 (10 mL) was then added at once, forming a black gummy solid. The mixture was stirred at room temperature for 30 minutes. The CH_2Cl_2 layer was decanted and concentrated *in vacuo*. Et_2O (100 mL) was added to the resulting residue and the insoluble solids were filtered. The filtrate was washed with water (100 mL), 5% $NaHCO_3$ (75 mL) and brine (75 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Subsequent chromatography of the residue on silica gel eluting with EtOAc/Hex (10-20%) afforded *t*-Butyl-4-(3-benzyloxycarbonyl-4-benzyloxybenzoyl)-3,5-dibenzyloxybenzoate (2.37 g, 70%) as a white foam.

4-(3-Benzyloxycarbonyl-4-benzyloxybenzoyl)-3,5-dibenzyloxybenzoic acid

Formic acid (25 mL, 96%) was added to *t*-Butyl-4-(3-benzyloxycarbonyl-4-benzyloxybenzoyl)-3,5-dibenzyloxybenzoate (2.33 g, 3.17 mmoL). The solid dissolved as it stirred at room temperature for 3 h. Water (100 mL) was added and the resulting white precipitate was collected by filtration then dried *in vacuo* at 60°C to afford 4-(3-Benzyloxycarbonyl-4-benzyloxybenzoyl)-3,5-dibenzyloxybenzoic acid (1.39 g, 65%) as a white solid. m.p. 137-138°C.



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4-R*-(4-(3-Benzyloxycarb nyl-4-benzyloxybenzoyl)-3,5-dibenzyloxybenzoyloxy)-3-R*-(4-benzyloxybenzamido)-N-benzylazepine (COMPOUND 693)

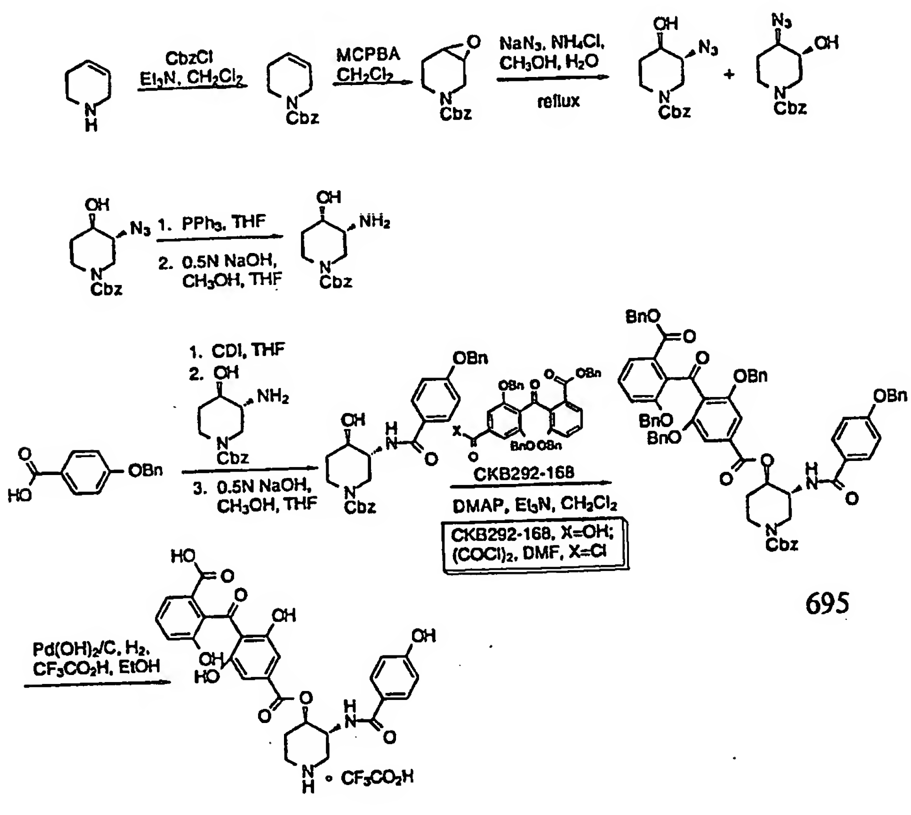
Oxalyl chloride (667 µL, 2.0 M) in CH_2Cl_2 was added to a stirred solution of 4-(3-Benzyloxycarbonyl-4-benzyloxybenzoyl)-3,5-dibenzyloxybenzoic acid (0.452 g, 0.67 mmoL) and N,N-DMF (0.5 mL) in CH_2Cl_2 (6 mL) at room temperature under N_2. The resulting solution was stirred at room temperature for 1 h and was then concentrated *in vacuo*. A solution of the resulting residue in CH_2Cl_2 (6 mL) was then added to a stirred solution of 4-R*-hydroxy-3-R*-(4-benzyloxybenzamido)-N-benzylazepine (0.286 g, 0.67 mmoL, for synthesis of see Compound 510), Et_3N (278 µL, 2.00 mmoL), and 4-DMAP (0.098 g, 0.80 mmoL) in CH_2Cl_2 (4 mL) at 0°C under N_2. The resulting orange solution was allowed to warm to room temperature as it stirred for 16 h. The solution was concentrated and the residue chromatographed on silica gel eluting with EtOAc/Hex (30-70%) affording Compound 693 (0.438 g, 60%) as a white gummy solid.

4-R*-(4-(3-Carboxy-4-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy)-3-R*-(4-hydroxybenzamido)azepine trifluoroacetic acid mono hydrate (COMPOUND 694)

A solution of 4-R*-(4-(3-Benzyloxycarbonyl-4-benzyloxybenzoyl)-3,5-dibenzyloxybenzoyloxy)-3-R*-(4-benzyloxybenzamido)-N-benzylazepine (0.120 g, 0.1410 mmol) in EtOH (6 mL), MeOH (8 mL) and TFA (0.75 mL) was added to moist palladium hydroxide on carbon (12 mg, 20% Pd). The mixture was stirred under 1 atm. 50 psi of hydrogen for 16 h. The mixture was filtered through a pad of celite and the filtrate concentrated *in vacuo*. The residue was chromatographed on a 21x250 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0 - 50% B over 60 m; flow: 15 mL/m) affording the title compound (0.071 g, 97%) as a yellow solid after lyophilization. m.p. >200°C.

IR (KBr, cm^{-1}): 3445, 2362, 1652, 1509, 1205, 669 cm^{-1}. Anal. Calcd. for $C_{30}H_{27}N_2O_8$ ∘ $1.5CF_3CO_2H$ ∘ H_2O: C, 50.35; H, 4.02; N, 3.79. Found: C, 50.18; H, 4.02; N, 4.27.

Anti-4-[4-(2-Hydroxycarbonyl-6-hydroxybenzoyl]-3,5-dihydroxybenzoyloxy)-3-(4-hydroxybenzamido)-piperidine trifluoroacetic acid salt (COMPOUND 696)



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696

To a chilled solution (0-5°C) of 1,2,3,6-tetrahydropyridine (15.0 g, 0.18 mol) and diisopropylethylamine (70.0 g, 0.54 mol) in methylene chloride (300 mL) under nitrogen atmosphere was added benzyl chloroformate (33.7 g, 0.20 mol) dropwise *via* an addition funnel. The reaction was stirred for 1 hour at 5°C, warmed to room temperature and stirred for an additional 18 hours, diluted with methylene chloride (150 mL) and water (100 mL), and the layers separated. The organic phase was then washed with 1N HCl (50 mL), water (50 mL), saturated sodium bicarbonate solution (50 mL), and brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude red oil was purified on a flash column (6:1-hexane: ethyl acetate) to produce carbamate as a colorless oil (37.9 g) in 97% yield.

Meta-chloroperbenzoic acid (80%, 12.4 g, 59.9 mmol) was added in small portions to a cooled solution (0-5°C) of olefin produced in the previous reaction (10 g, 46.1 mmol) in 50 mL methylene chloride under nitrogen atmosphere. After 30 minutes, the cooling bath was removed and the mixture was allowed to stir at room temperature for 18 hours. The white suspension was diluted with methylene chloride (300 mL) and washed with saturated sodium sulfite solution (2 x 30 mL), saturated sodium bicarbonate solution (2 x 50 mL), and brine (50 mL). The organic layer was then dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo* producing 10.7 grams (>95% yield) of epoxide as a clear, colorless oil, which was used without purification.

To a solution of epoxide produced in the previous reaction (5.5 g, 23.6 mmol) in methanol-water (125 mL and 20 mL, receptively) was added sodium azide (9.3 g, 142 mmol) and ammonium chloride (3.8 g, 70.8 mmol) in one portion. The solution was heated at reflux for 20 hours, cooled to room temperature, and the methanol evaporated with reduced pressure. The remaining aqueous layer was diluted with 0.5 N sodium hydroxide solution (100 mL), extracted with methylene chloride (3 x 100 mL), and the combined organic

layers washed with water (50 mL), and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and the solvent removed *in vacuo*. The resulting mixture of regioisomeric azidoalcohols were separated by flash column chromatography to yield 3-azido (4.5 g, R_F 0.21) and 4-azido isomers (1.0 g, R_F 0.19) as white solids in 83% combined yield.

To a stirred solution of the 3-azido alcohol (12.2 mmol, 3.4 g) in anhydrous tetrahydrofuran (THF, 100 mL) at room temperature (nitrogen atmosphere) was added triphenylphosphine (13.4 mmol, 3.5 g) in one portion. The colorless solution was stirred for 18 hours, concentrated *in vacuo*, and the resulting viscous oil taken up in methanol (50 mL). Sodium hydroxide solution (0.5 N NaOH, 50 mL) was then added, and the mixture was stirred at room temperature for 24 hours (Note 1: white precipitate forms during the hydrolysis). The solvent was then removed *in vacuo* and the crude material taken up in chloroform ($CHCl_3$, 250 mL) and water (50 mL), and the organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Aminoalcohol was purified *via* column chromatography and isolated in 86% purified yield (2.6 g) as a white solid.

Carbonyldiimidazole (CDI, 2.01 mmol, 330 mg) and 4-benzyloxybenzoic acid (2.01 mmol, 460 mg) were dissolved in THF (10 mL) and the colorless solution stirred at room temperature under a nitrogen atmosphere for 1 hour. A solution of amino alcohol produced in the previous reaction (1.34 mmol, 335 mg) in methylene chloride (10 mL) was then added and the mixture stirred for an additional 18 hours. The crude material was then concentrated, and taken up in THF/methanol (20 mL/20 mL). After adding sodium hydroxide solution (0.5 N NaOH, 5 mL), the mixture was stirred at room temperature for 2 hours and concentrated. The crude reaction mixture was then partitioned between $CHCl_3$ and water, and the organic layer washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Hydroxyamide was purified by slow trituration from methylene chloride /

hexane at room temperature and isolated as a white solid (530 mg) in 61% yield.

COMPOUND 695

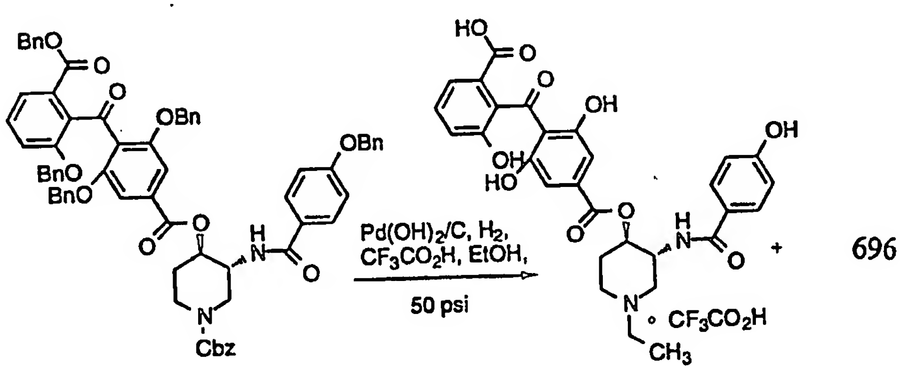
To a chilled (ice/water bath) and stirred solution of benzophenone acid (0.45 mmol, 309 mg) in methylene chloride (5 mL) under a nitrogen atmosphere was added oxalyl chloride ($(COCl)_2$, 0.68 mmol, 87 mg), and N,N-dimethylformamide (DMF, catalytic, 2 drops), and the red-brown solution was stirred under the same conditions for 60 minutes. The resulting acid chloride was then concentrated *in vacuo* and stored at reduced pressure until needed. In a separate flask, hydroxyamide produced in the previous reaction (0.48 mmol, 215 mg) was added to methylene chloride (5 mL) and the white slurry was stirred at room temperature under a nitrogen atmosphere. Triethylamine (Et_3N, 1.14 mmol, 115 mg) and 4-dimethylaminopyridine (DMAP, catalytic, = 2 mg) were added. A solution of the acid chloride (see above) in methylene chloride (5 mL) was then added in one portion and the resulting red-brown solution was stirred at room temperature overnight (15-18 hours). The now deep-red solution was transferred to a separatory funnel, diluted with methylene chloride (100 mL), washed with saturated sodium bicarbonate solution (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting red-brown foam was chromatographed on a silica column (3:1-hexane: ethyl acetate), and perbenzylated intermediate was isolated (350 mg, 69% yield, purified) as a yellow solid.

COMPOUND 696

Perbenzylated intermediate Compound 695 (0.27 mmol, 300 mg) was dissolved in ethyl acetate (EtOAc, 6 mL) and placed in a 100 mL 3-necked round-bottomed flask equipped with a nitrogen inlet, a hydrogen balloon, and a gas release valve. Absolute ethanol (15 mL), Pearlman's catalyst ($Pd(OH)_2$ on carbon, 20% palladium by weight, 50-75 mg) and trifluoroacetic acid (TFA, 2 drops) were then added, and the

reaction flask purged with nitrogen gas, followed by hydrogen gas. After stirring for 18 hours, the reaction mixture was diluted with ethanol (10 mL) and filtered over a pad of celite, the celite was washed well with ethanol, and the resulting bright yellow solution was concentrated *in vacuo*. Compound 696 was purified *via* HPLC (41 x 300 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient 0-50% B over 60 minutes, flow: 25 mL/min, retention time = 36.5 minutes). The purified fractions were concentrated and lyophilized from water to give 60 mg (50% yield, purified) of the title compound as a yellow fluffy solid. IR (KBr): 1720, 1677, 1636, 1607, 1510, 1428, 1376, 1234 cm^{-1}; EA (calculated for $C_{27}H_{24}N_2O_{10}$ ∘ 0.9 $C_2HF_3O_2$ ∘ 2.9 H_2O): C, 50.03; H, 4.48; N, 4.05. Found: C, 50.09; H, 4.54; N, 4.06. MS (m/e, low resolution FAB): $[M + H]^+$ = 537.

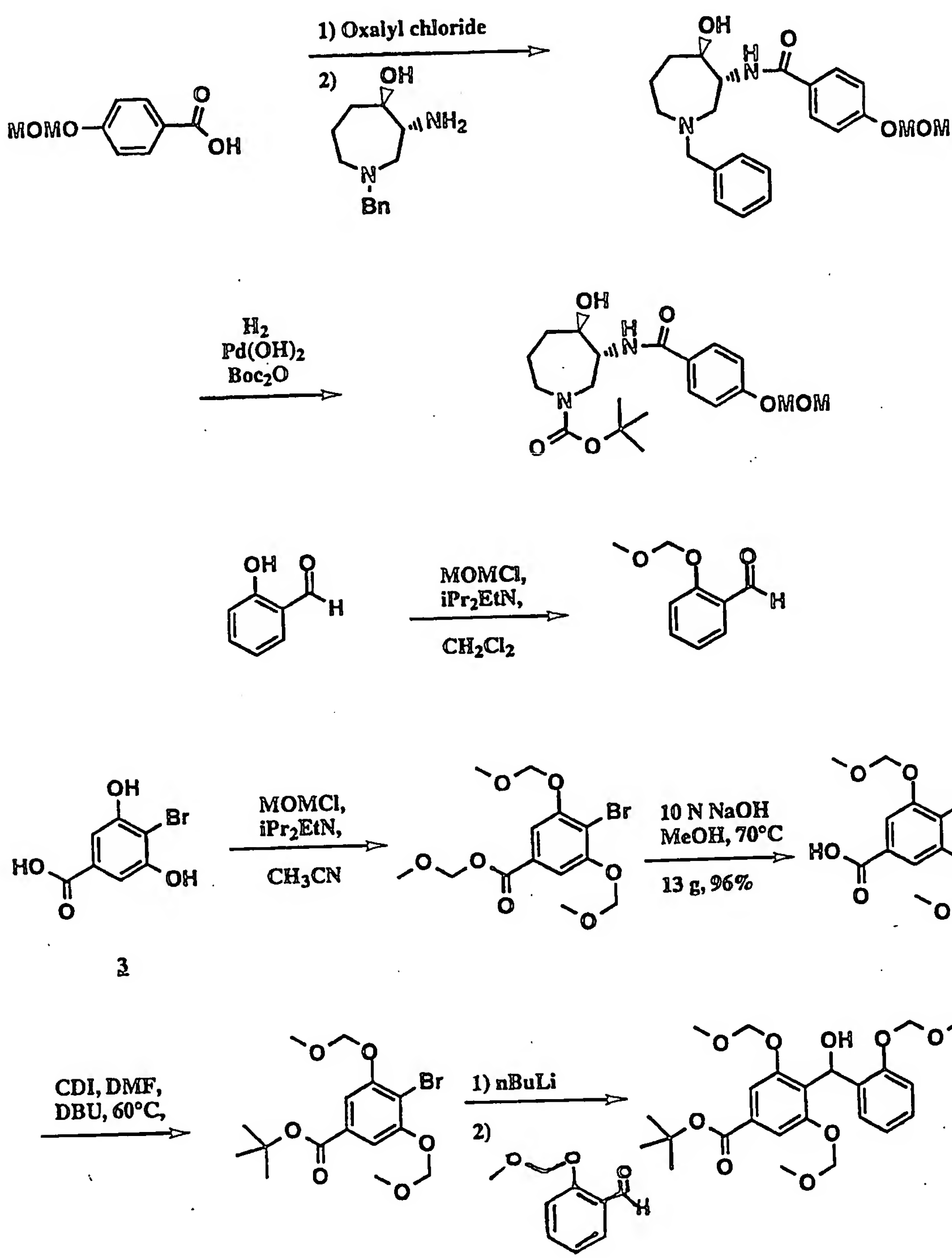
Anti-N-Ethyl-4-[4-(2-hydroxycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-3-(4-hydroxybenzamido)-piperidine trifluoroacetic acid salt (COMPOUND 697)



695 697

Perbenzylated intermediate Compound 695 (0.27 mmol, 300 mg) was dissolved in ethyl acetate (EtOAc, 6mL) and placed in a 100 mL 3-necked round-bottomed flask equipped with a nitrogen inlet, a hydrogen balloon, and a gas release valve. Absolute ethanol (15 mL), Pearlman's catalyst ($Pd(OH)_2$ on carbon, 20% palladium by weight, 50-75 mg) and trifluoroacetic acid (TFA, 2 drops) were then added, and the reaction flask purged with nitrogen gas, followed by hydrogen gas. After stirring for 18 hours, the reaction mixture was diluted with ethanol (10 mL) and filtered over a pad of celite, the celite was washed well with ethanol, and the resulting bright yellow solution was concentrated *in vacuo*. Balanol analogue Compound 697, a minor product from the hydrogenolysis reaction, was isolated and purified *via* HPLC (41 x 300 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient 0-50% B over 60 minutes, flow: 25 mL/min, retention time = 39.6 minutes). The purified fractions were concentrated and lyophilized from water to give 10.1 mg (8% yield, purified) of Compound 697 as a yellow fluffy solid. IR (KBr): 1707, 1687, 1676, 1629, 1607, 1512, 1427, 1369, 1281, 1230, 1202 cm^{-1}; EA (calculated for $C_{29}H_{28}N_2O_{10}$ • 1.5 $C_2HF_3O_2$ • 3.0 H_2O): C,48.68; H, 4.53; N, 3.55. Found: C, 48.64; H, 4.39; N, 3.49. MS (m/e, low resolution FAB): $[M + H]^+$ = 565; $[M + Na]^+$ = 587.

(±)-*Anti*-4-[4-(2-hydroxybenzoyl)-3,5-dihydroxybenzyloxy]-3-(4-hydroxybenzamido)perhydroazepine, trifluoroacetic acid salt (COMPOUND 699)



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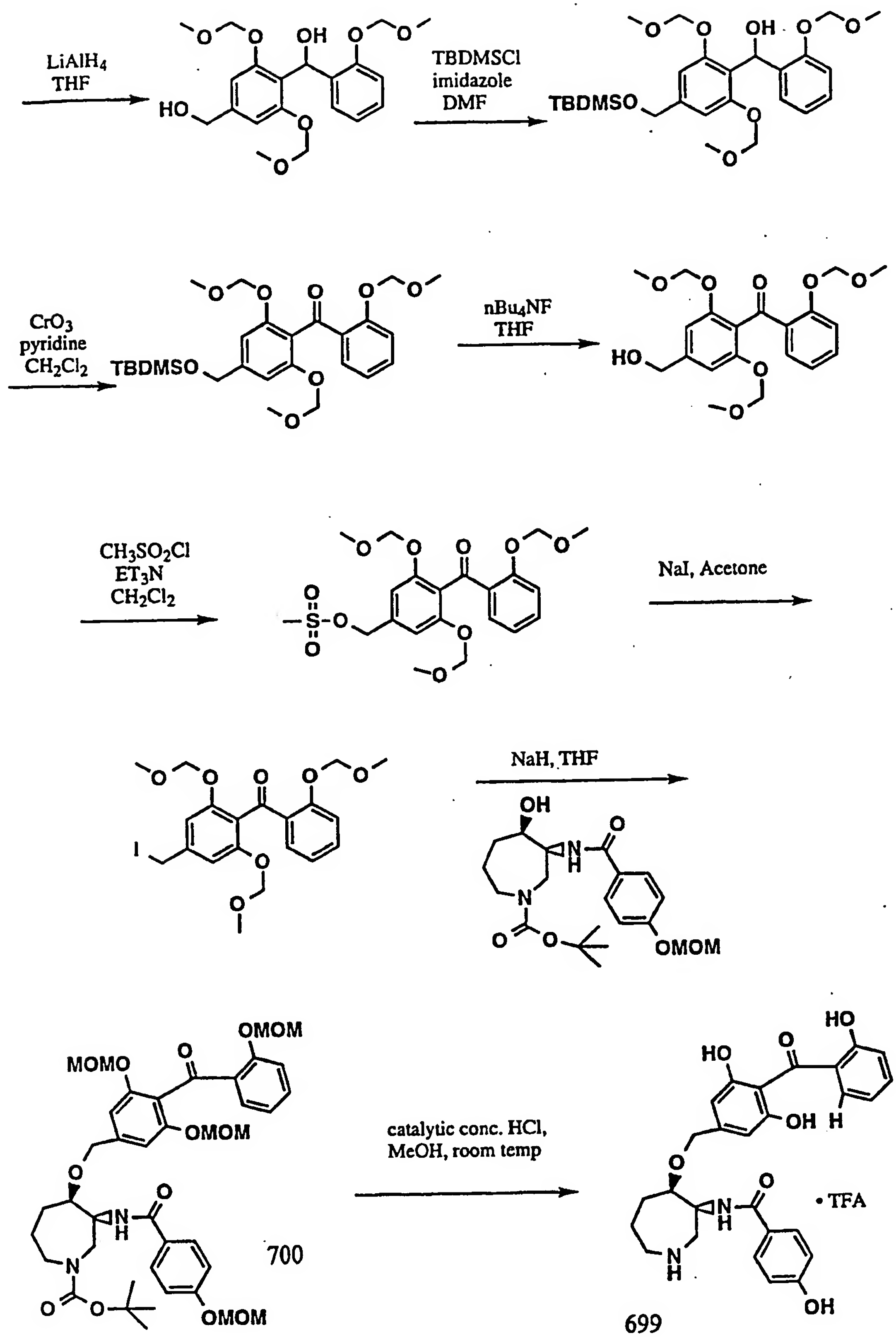

LiAlH4
THF
TBDMSCl
imidazole
DMF
CrO3
pyridine
CH2Cl2
nBu4NF
THF
CH3SO2Cl
ET3N
CH2Cl2
NaI, Acetone
NaH, THF
OMOM
catalytic conc. HCl,
MeOH, room temp
• TFA
700
699

(±)-*anti*-4-hydroxy-3-(4-methoxymethyleneoxybenzamido)-N-benzylperhydroazepine

To a solution of the 4-methoxymethyleneoxybenzoic acid (1.85 g, 10.2 mmol, for preparation see Compound 728) in anhydrous CH_2Cl_2 (40 mL) under an atmosphere of nitrogen at 0°C was added oxalyl chloride (10.2 ml, 10.2 mmol) dropwise. The reaction mixture was allowed to stir at 0°C for 1 h. The volatiles were removed under reduced pressure and the residue was dried under full vacuum at room temperature for 1 h.

To a solution of (±)-trans-3-amino-4-hydroxy-N-benzylperhydroazepine (2.0 g, 9.70 mmol, and triethylamine (2.70 mL, 19.0 mmol) in anhydrous THF (20 mL) under an atmosphere of nitrogen at 0°C was added a solution of the above generated acid chloride in THF and the mixture was allowed to stir while warming to room temperature overnight. The volatiles were removed under reduced pressure. The reaction mixture was diluted with ethyl acetate and washed with distilled water and brine. The ethyl acetate layer was dried over $MgSO_4$, filtered and the volatiles were removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 10:1 hexane: ethyl acetate - 1:1 hexane: ethyl acetate) to provide a partially purified oil, the title compound (±)-*anti*-4-hydroxy-3-(4-methoxymethyleneoxybenzamido)-N-benzylazepine (2.15 g, 62%) which was used in the next reaction.

(±)-*anti*-4-hydroxy-3-(4-methoxymethyleneoxybenzamido)-N-*t*-butyloxycarbonylperhydroazepine

To a solution of (±)-*anti*-4-hydroxy-3-(4-methoxymethyleneoxybenz-amido)-N-benzylperhydroazepine, (1.00 g, 2.81 mmol) and di-tert-butyl dicarbonate (1.53 g, 7.00 mmol) in 1:1 ethyl acetate:ethanol (100 mL) under an atmosphere of nitrogen was added $Pd(OH)_2$ (0.20 g, 20% by wt, 20% on C). The reaction mixture was placed under H_2 (40 psi) overnight. The reaction mixture was filtered through a pad of silica gel and the volatiles were removed under reduced pressure to provide a partially purified oil, of the title

compound (±)-*anti*-4-hydroxy-3-(4-methoxymethyleneoxybenzamido)-N-*t*-butyloxycarbonylperhydroazepine (0.60 g, 54%) which was used as is in the next reaction.

2-Methoxymethyleneoxybenzaldehyde

To a solution of the salicylaldehyde (3.00 g, 24.6 mmol) in CH_2Cl_2 (30 mL) under an atmosphere of nitrogen at 0°C was added N,N-diisopropylethylamine (23.5 ml, 0.134 mol) followed by the dropwise addition of a solution of chloromethyl methyl ether (10.1 mL, 0.134 mol) in acetonitrile (30 mL) over 1 h. The reaction mixture was allowed to stir at 0°C for 1.5 h and then allowed to warm to room temperature while stirring overnight. The reaction mixture was quenched with sat'd NH_4Cl (60 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 60 mL). The combined CH_2Cl_2 layers were dried over $MgSO_4$, filtered and the volatiles were removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20:1 hexane:ethyl acetate) to provide a colorless oil, of the title compound (3.80 g, 93%).

Methoxymethyleneoxy 4-bromo-3,5-dimethoxymethyleneoxybenzoate

To a solution of the 4-bromo-3,5-dihydroxyoxy benzoic acid (10.0 g, 42.9 mmol) in acetonitrile (160 mL) under an atmosphere of nitrogen at 0°C was added N,N-diisopropylethylamine (40.9 ml, 0.235 mol) followed by the dropwise addition of a solution of chloromethyl methyl ether (17.6 mL, 0.233 mol) in acetonitrile (40 mL) over 2 h. The reaction mixture was allowed to stir at 0°C for 1 h and then allowed to warm to room temperature while stirring overnight. The volatiles were removed under reduced pressure and the residue was partitioned between ethyl acetate and 1:1 sat'd NH_4Cl:distilled water. The aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined ethyl acetate layers were washed with distilled water (2 x 50 mL) and brine. The ethyl acetate layer was dried over $MgSO_4$,

filtered and the volatiles were removed under reduced pressure to provide a brown solid of the title compound (15.2 g, 97%). ^{1}H NMR ($CDCl_3$) δ 7.53 (s, 2H), 5.48 (s, 2H), 5.32 (s, 4H), 3.55 (s, 3H), 3.54 (s, 6H).

4-Bromo-3,5-dimethoxymethyleneoxybenzoic acid

To a solution of methoxymethyleneoxy 4-bromo-3,5-dimethoxymethyleneoxybenzoate (15.2 g, 41.6 mmol) in methanol was added 10N NaOH (100 mL) and the reaction mixture was heated at 70°C for 3 h. After cooling to room temperature the reaction mixture was acidified with 1N HCl. The reaction mixture was extracted with ethyl acetate (2 times). The combined ethyl acetate layers were washed with water and brine. The ethyl acetate layer was dried over anhydrous magnesium sulfate, filtered, and the volatiles were removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, 3:1 ethyl acetate: hexane) which provided a white solid of the title compound (13.0 g, 96%). ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 2H), 5.33 (s, 4H), 3.55 (s, 6H).

t-butyl 4-Bromo-3,5-dimethoxymethyleneoxybenzoate

To a solution of 4-Bromo-3,5-dimethoxymethyl eneoxybenzoic acid (13.0 g, 40.0 mmol) in anhydrous DMF under an atmosphere of nitrogen was added CDI (11.1 g, 68.0 mol) and the reaction mixture was heated at 70°C for 1 h. To the reaction mixture was added t-BuOH (15.4 mL, 160 mmol) and DBU (10.3 mL, 68.0 mmol) and the reaction mixture was allowed to stir at 70°C for 3 h. The reaction mixture was diluted with ethyl acetate and washed with 1N HCl (80 mL), distilled water, 1N NaOH, and brine. The ethyl acetate layer was dried over anhydrous $MgSO_4$, filtered and the volatiles were removed under reduced pressure. Trituration of the crude product with 20:1 hexane: ethyl acetate followed by filtration provided a white solid of the title compound (13.4 g, 89%). 1H NMR ($CDCl_3$) 7.43 (s, 2H), 5.30 (s, 4H), 3.54 (s, 6H), 1.59

(s, 9H). Anal. Calcd for $C_{15}H_{21}O_6$: C, 47.76; H, 5.61. Found: C, 47.72; H, 5.70.

To a solution of the *t*-butyl 4-Bromo-3,5-dimethoxy methyleneoxybenzoate (4.52 g, 12.0 mmol) in anhydrous THF (45 mL, Aldrich) under an atmosphere of nitrogen with an internal temperature of -70°C was added n-butyllithium (7.2 mL, 14.4 mmol, 2M in cyclohexane) dropwise over 0.5 h. The reaction mixture was allowed to slowly warm to -40°C and the mixture was stirred at -40°C for 1.5 h. The solution was recooled to -70°C and a solution of 2-methoxymethyleneoxybenzaldehyde (2.47 g, 14.9 mmol) in THF was added dropwise over 15 minutes and the mixture was allowed to stir and warm to to -40°C for 1.5 h. The volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate and distilled water. The layers were separated and the pH of the aqueous phase was adjusted to 7 with 1N HCl. The aqueous phase was extracted with ethyl acetate (2 x 90 mL). The combined ethyl acetate layers were washed with distilled water and brine. The ethyl acetate layer was dried over anhydrous $MgSO_4$, filtered and the volatiles were removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20:1 petroleum ether: ether - 4:1 petroleum ether: ether) which provided a colorless oil of the ester (3.5 g, 63%). Anal. Calcd for $C_{24}H_{32}O_9$: C, 62.06; H, 6.94. Found: C, 61.80; H, 7.23.

To a solution of the ester of the previous reaction (2.60 g, 5.60 mmol) in anhydrous THF (25 mL) under an atmosphere of nitrogen at 0°C was added $LiAlH_4$ (14 mL, 0.014 mmol, 1M in THF) dropwise over 20 minutes. The reaction mixture was allowed to warm to room temperature and stirring was continued for 48 h. The reaction mixture was quenched by the successive dropwise additions of distilled water (0.53 mL), 15% NaOH (0.53 ml), and distilled water (1.60 mL). Filtration of the heterogeneous mixture followed by removal of the volatiles under reduced pressure provided a white solid of alcohol (2.20 g, 98%). Anal. Calcd for $C_{20}H_{26}O_8$: C, 60.90; H, 6.64. Found: C, 60.57; H, 6.67.

To a solution of the alcohol of the previous reaction (2.08 g, 5.26 mmol) in anhydrous DMF (36 mL) under an atmosphere of nitrogen was added TBDMSCl (0.79 g, 5.26 mmol) followed by imidazole (0.38g, 5.50 mmol) and the reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was diluted with ethyl acetate and washed with distilled water. The ethyl acetate layer was dried over anhydrous magnesium sulfate, filtered, and the volatiles were removed under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, 5:1 hexane ethyl acetate - 1:2 hexane:ethyl acetate) which provided a viscous oil of the alcohol (1.66 g, 62%). Anal. Calcd for $C_{26}H_{40}O_8Si$: C, 61.39; H, 7.93. Found: C, 61.11; H, 7.98.

To a solution of pyridine (2.60 mL, 3.21 mmol) in anhydrous CH_2Cl_2 (40 mL) was added CrO_3 (1.60g, 16 mmol) in one portion and the mixture was allowed to stir for 15 minutes. A solution of the alcohol of the previous reaction (1.36 g, 2.67 mmol) in anhydrous CH_2Cl_2 (4.5 mL) was added all at once and a tarry black deposit separated immediately. After stirring an additional 15 minutes the CH_2Cl_2 layer was decanted and the volatiles were removed under reduced pressure. The residue was taken up in ether, filtered, and washed with 1N NaOH, and brine. The ether layer was dried over anhydrous magnesium sulfate, filtered, and the volatiles were removed under reduced pressure to provide a white solid of the silyl ether (1.20 g, 89%). Anal. Calcd for $C_{26}H_{38}O_8Si$: C, 61.64; H, 7.56. Found: C, 61.29; H, 7.55.

(±)-*Anti*-4-[4-(2-methoxymethyleneoxybenzoyl)-3,5-dimethoxymethyleneoxybenzyloxy]-3-(4-methoxymethyl eneoxybenzamido)-N-*t*-butyloxycarbonylperhydroazepine (COMPOUND 700)

To a solution of the silyl ether of the previous reaction (307 mg, 6.06 mmol) in anhydrous THF (3 mL) under an atmosphere of nitrogen was added tetrabutylammonium fluoride (1.21 mL, 1.21 mmol, 1M in THF) dropwise over 5 minutes. The

reaction mixture was allowed to stir for 2 h at room temperature and then the volatiles were removed under reduced pressure. The residue was diluted with ethyl acetate (150 mL) and washed with water (3 x 50 mL) and brine (30 mL). The ethyl acetate layer was dried over anhydrous magnesium sulfate, filtered, and the volatiles were removed under reduced pressure which provided a light yellow solid of the alcohol (236 mg, 99%).

To a solution of the alcohol of the previous reaction (200 mg, 0.526 mmol) in anhydrous dichloromethane (15 mL) under an atmosphere of nitrogen at 0°C was added triethylamine (146 μL, 1.05 mmol) followed by a solution of methanesulfonyl chloride (45 μL, 0.578 mmol) in anhydrous dichloromethane dropwise over 10 minutes. The reaction mixture was allowed to warm to room temperature while stirring over 1 h. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with distilled water (40 mL) and brine (25 mL). The ethyl acetate layer was dried over anhydrous $MgSO_4$, filtered and the volatiles were removed under reduced pressure which provided a light yellow oil of the mesylate (0.233 g, 94%).

To a solution of the crude mesylate obtained above (0.233g, 0.495 mmol) in HPLC grade acetone (20 mL, Aldrich) was added sodium iodide (248 mg, 1.65 mmol) under an atmosphere of nitrogen and the reaction mixture was allowed to stir for 1 h at room temperature. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with distilled water (2 x 10 mL) and brine (30 mL). The ethyl acetate layer was dried over anhydrous $MgSO_4$, filtered and the volatiles were removed under reduced pressure which provided a light yellow oil of the iodide (210 mg, 84%).

To a suspension of sodium hydride (20 mg, 0.833 mmol, 60% in mineral oil) in anhydrous THF (2 mL) under an atmosphere of nitrogen at 0°C was added a solution of the alcohol (70 mg, 0.177 mmol, 4-hydroxy-3-MOMO-benzamide alcohol) in anhydrous THF (3 mL) dropwise over 15 minutes. The reaction mixture was allowed to stir while warming to

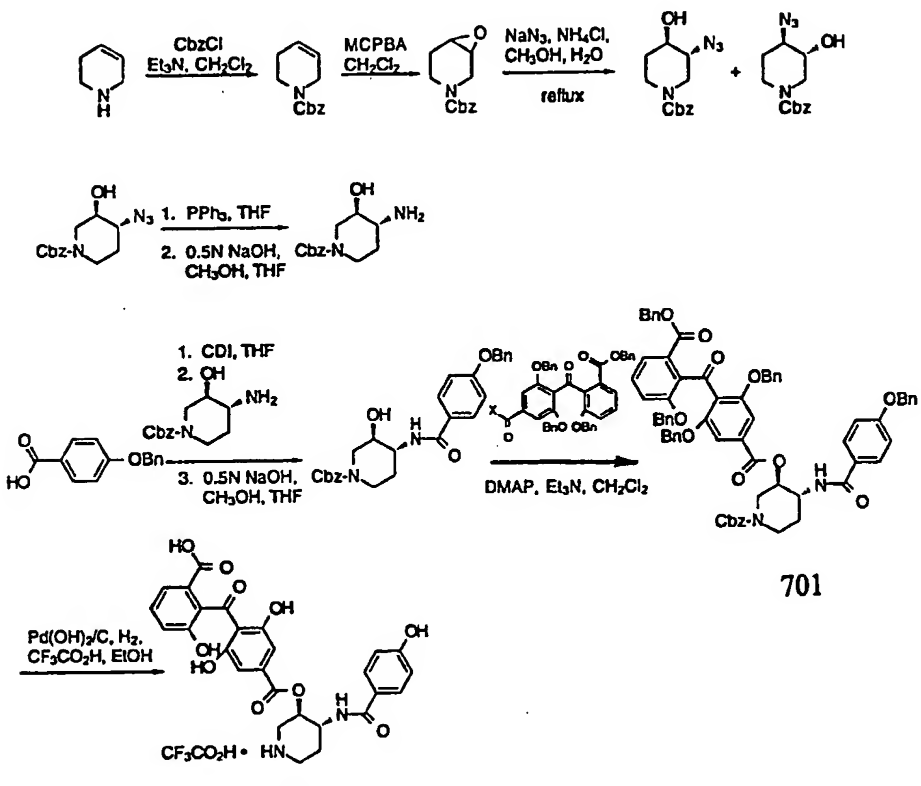
room temperature over 1 h during which time the reaction became a nearly clear homogeneous solution. A solution of the above generated iodide (100 mg, 0.199 mmol) in freshly distilled anhydrous THF (3 mL) was added dropwise over 20 minutes. The reaction mixture was allowed to stir for 4 h at room temperature. The volatiles were removed under reduced pressure. The residue was diluted with ethyl acetate and washed with distilled water and brine. The ethyl acetate layer was dried over anhydrous $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 3:1 hexane:ethyl acetate) to provide a colorless oil which was further purified on a Dynamax-60 C18 column (21 mm ID X 30 cm length) using a linear gradient from 50% A (0.1% TFA and 5% acetonitrile in water) to 100% B (pure acetonitrile) over 60 m at 15 mL/min. The product elutes in 20 minutes. Removal of the volatiles under reduced pressure provided the title compound as a white solid (COMPOUND 700) (48 mg, 35%).

(±)-*Anti*-4-[4-(2-hydroxybenzoyl)-3,5-dihydroxybenzyloxy]-3-(4-hydroxybenzamido)perhydroazepine, trifluoroacetic acid salt (COMPOUND 699)

To a solution of (±)-anti-4-[4-(2-methoxymethyleneoxybenzoyl)-3,5-dimethoxymethyleneoxybenzyloxy]-3-(4-methoxymethyleneoxybenzamido)-N-*t*-butyloxycarbonylperhydroazepine (48 mg, 62.5 μmol, COMPOUND 700) in methanol (12 mL) was added conc. HCl (35 drops) at room temperature and the reaction mixture was allowed to stir for 5 h. The volatiles were removed under reduced pressure. The product was chromatographed on a Dynamax-60 C18 column (21 mm ID X 30 cm length) using a linear gradient from 100% A (0.1% TFA and 5% acetonitrile in water) to 50% B (pure acetonitrile) over 60 m at 15 mL/min. The product elutes in 28 minutes. Removal of the volatiles under reduced pressure provided Compound 699 as a white solid (38 mg, 90%), mp 140-143°C. IR KBr (disc) cm^{-1} 3424, 3274, 2886, 2875, 1677,

1625, 1544, 1508, 1435, 1398, 1365, 1278, 1243, 1203, 1140, 1107, 1057, 1036, 987, 956, 933, 912, 845, 762, 723, 669, 601. Anal Calcd for $C_{27}H_{28}N_2O_9 \cdot C_2HF_3O_2 \cdot 0.5\ H_2O$: C, 53.58; H, 4.57; N, 4.17. Found: C, 53.80; H, 4.91; N, 4.34.

Anti-3-[4-(2-Hydroxycarbonyl-6-hydroxybenzoyl]-3,5-dihydroxybenzoyloxy)-4-(4-hydroxybenzamido)-piperidine trifluoroacetic acid salt (COMPOUND 702)



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To a chilled solution (0-5°C) of 1,2,3,6-tetrahydropyridine (15.0 g, 0.18 mol) and diisopropylethyl amine (70.0 g, 0.54 mol) in methylene chloride (300 mL) under nitrogen atmosphere was added benzyl chloroformate (33.7 g, 0.20 mol) dropwise *via* an addition funnel. The reaction was stirred for 1 hour at 5°C, warmed to room temperature and stirred for an additional 18 hours, diluted with methylene chloride (150 mL) and water (100 mL), and the layers separated. The organic phase was then washed with 1N HCl (50 mL), water (50 mL), saturated sodium bicarbonate solution (50 mL), and brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude red oil was purified on a flash column (6:1-hexane: ethyl acetate) to produce carbamate olefin as a colorless oil (37.9 g) in 97% yield.

Meta-Chloroperbenzoic acid (MCPBA) (80%, 12.4 g, 59.9 mmol) was added in small portions to a cooled solution (0-5°C) of carbamate/olefin (10 g, 46.1 mmol) in 50 mL methylene chloride under nitrogen atmosphere. After 30 minutes, the cooling bath was removed and the mixture was allowed to stir at room temperature for 18 hours. The white suspension was diluted with methylene chloride (300 mL) and washed with saturated sodium sulfite solution (2 x 30 mL), saturated sodium bicarbonate solution (2 x 50 mL), and brine (50 mL). The organic layer was then dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo* producing 10.7 grams (>95% yield) of epoxide as a clear, colorless oil, which was used without purification.

To a solution of epoxide from the previous reaction (5.5 g, 23.6 mmol) in methanol - water (125 mL and 20 mL, receptively) was added sodium azide (9.3 g, 142 mmol) and ammonium chloride (3.8 g, 70.8 mmol) in one portion. The solution was heated at reflux for 20 hours, cooled to room temperature, and the methanol evaporated with reduced pressure. The remaining aqueous layer was diluted with 0.5 N sodium hydroxide solution (100 mL), extracted with methylene chloride (3 x 100 mL), and the combined organic layers washed

with water (50 mL), and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and the solvent removed *in vacuo*. The resulting mixture of regioisomeric azidoalcohols were separated by flash column chromatography to yield 3-azido (4.5 g, R_F 0.21) and 4-azido alcohols (1.0 g, R_F 0.19) as white solids in 83% combined yield.

To a stirred solution of 4-azidoalcohol (5.80 mmol, 1.6 g) in anhydrous tetrahydrofuran (THF, 100 mL) at room temperature (nitrogen atmosphere) was added triphenylphosphine (PPh_3, 6.40 mmol, 1.7 g) in one portion. The colorless solution was stirred for 18 hours, concentrated *in vacuo*, and the resulting viscous oil taken up in methanol (50 mL). Sodium hydroxide solution (0.5 N NaOH, 50-100 mL) was then added, and the mixture was stirred at room temperature for 24 hours (Note 1: white precipitate forms during the hydrolysis). The solvent was then removed *in vacuo* and the crude material taken up in chloroform ($CHCl_3$, 150 mL) and water (50 mL), and the organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The aminoalcohol reaction product was purified *via* column chromatography and isolated in 77% purified yield (1.1 g) as a white solid.

Carbonyldiimidazole (CDI, 3.0 mmol, 490 mg) and 4-benzyloxybenzoic acid (3.0 mmol, 685 mg) were dissolved in THF (20 mol) and the colorless solution stirred at room temperature under a nitrogen atmosphere for 1.5 hours. A solution of amino alcohol from the previous reaction (2.0 mmol, 500 mg) in methylene chloride (20 mL) was then added and the mixture stirred for an additional 36 hours. The crude material was then concentrated, and taken up in THF/methanol (25 mL/25 mL). After adding sodium hydroxide solution (0.5N NaOH, 10 mL), the mixture was stirred at room temperature for 18 hours and concentrated. The crude reaction mixture was then partitioned between $CHCl_3$ (100 mL) and water (25 mL), and the organic layer washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting hydroxyamide was

purified by slow trituration from methylene chloride/hexane at room temperature and isolated as a white solid (330 mg) in 36% yield.

COMPOUND 701

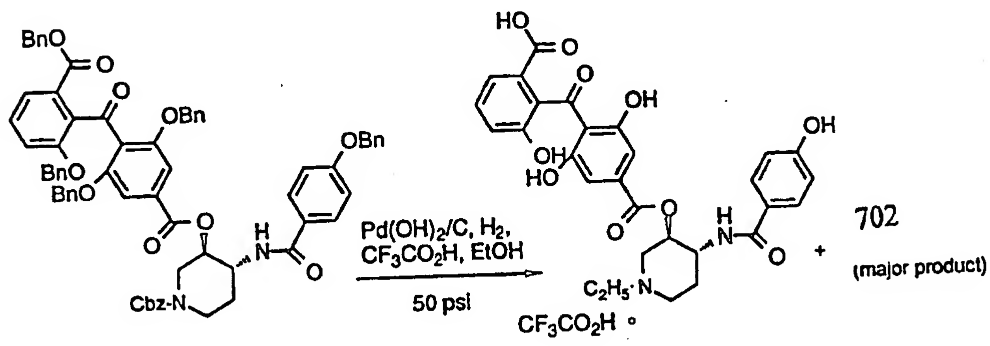
To a cooled (ice/water bath) stirred solution of benzophenone acid (0,45 mmol, 306 mg) in methylene chloride (5 mL) under a nitrogen atmosphere was added oxalyl chloride ($(COCl)_2$, 0.68 mmol, 87 mg), and N,N-dimethylformamide (DMF, catalytic, 2 drops), and the red-brown solution was stirred under the same conditions for 90 minutes. The resulting acid chloride was then concentrated *in vacuo* and stored at reduced pressure until needed. In a separate flask, hydroxyamide produced from the previous reaction (0.50 mmol, 228 mg) was added to methylene chloride (5 mL) and the white slurry was stirred at 0-5°C under a nitrogen atmosphere. Triethylamine (Et_3N, 1.14 mmol, 115 mg) and 4-dimethylaminopyridine (DMAP, catalytic, ≈ 2 mg) were added. A solution of the acid chloride (see above) in methylene chloride (5 mL) was then added over 60 seconds and the resulting red-brown solution was stirred at room temperature overnight (15-18 hours). The deep-red solution was transferred to a separatory funnel, diluted with methylene chloride (100 mL), washed with saturated sodium bicarbonate solution (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting red-brown foam was chromatographed on a silica column (3:1-hexane: ethyl acetate), and perbenzylated intermediate Compound 701 was isolated (420 mg, 83% yield, purified) as a yellow solid.

COMPOUND 702

Perbenzylated intermediate Compound 701 (0.36 mmol, 400 mg) was dissolved in ethanol/THF (EtOH/THF - 20 mL/5 mL) and placed in a 100 mL 3-necked round-bottomed flask equipped with a nitrogen inlet, a hydrogen balloon, and a gas release valve. Pearlman's catalyst ($Pd(OH)_2$ on carbon, 20% palladium by weight, 80 mg) and trifluoroacetic acid (TFA, 5 drops)

were then added, and the reaction flask purged with nitrogen gas, followed by hydrogen gas. After stirring for 20 hours, the reaction mixture was diluted with ethanol (20 mL) and filtered over a pad of celite, the celite was washed well with ethanol, and the resulting bright yellow solution was concentrated *in vacuo*. Compound 702 was purified *via* HPLC (41 x 300 mm C18 column (solvent A: 95:5 water / acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient 0-50% B over 60 minutes, flow: 25 mL/min, retention time = 35.7 minutes). The purified fractions were concentrated and lyophilized from water to give Compound 702 as a yellow fluffy solid in 53% (122 mg) purified yield. IR (KBr): 1698, 1681, 1608, 1509, 1426, 1365, 1236, 1201 cm^{-1}. EA (calculated for $C_{27}H_{24}N_2O_{10}$ • $1.2C_2HF_3O_2$ • $2.0H_2O$): C, 49.78; H, 4.15; N, 3.95. Found: C, 49.43; H, 4.16; N, 3.92. MS (m/e, low resolution FAB): $[M + H]^+$ = 537.

Anti-N-Ethyl-3-[4-(2-hydroxycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-4-(4-hydroxybenzamido)-piperidine trifluor acetic acid salt (COMPOUND 704)

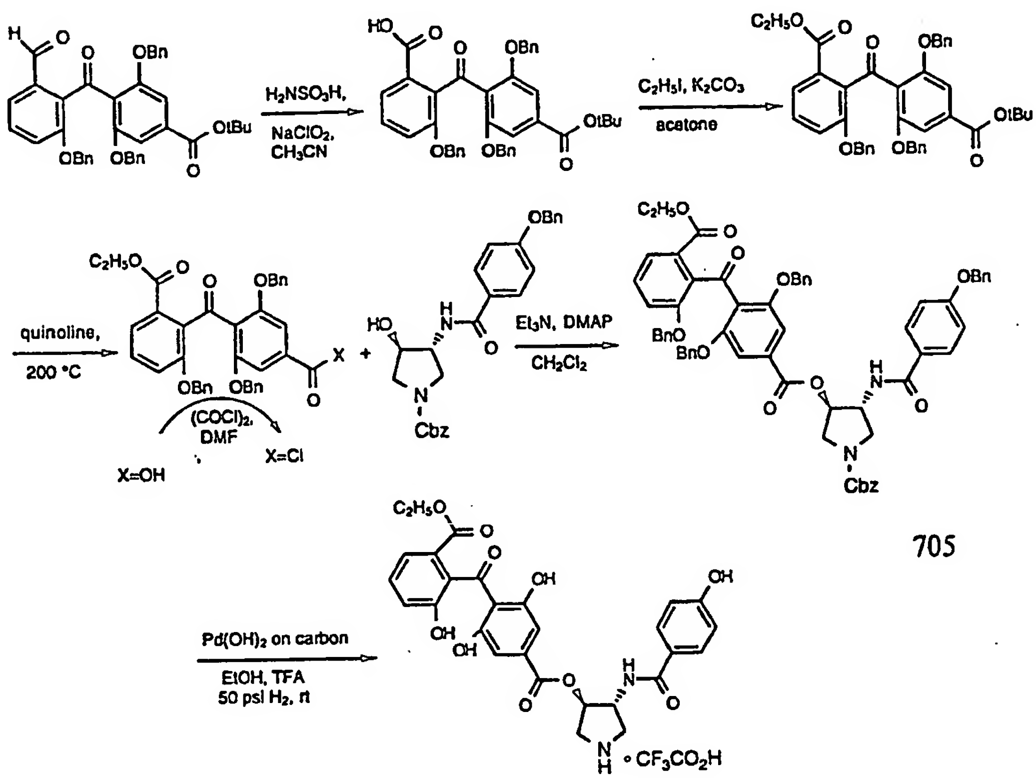


701 704

Perbenzylated intermediate Compound 701 (0.36 mmol, 400 mg) was dissolved in ethanol/THF (EtOH/THF - 20 mL/5 mL) and placed in a 100 mL 3-necked round-bottomed flask equipped with a nitrogen inlet, a hydrogen balloon, and a gas release valve. Pearlman's catalyst ($Pd(OH)_2$ on carbon, 20% palladium by weight, 80 mg) and trifluoroacetic acid (TFA, 5 drops) were then added, and the reaction flask purged with nitrogen gas, followed by hydrogen gas. After stirring for 20 hours, the reaction mixture was diluted with ethanol (20mL) and filtered over a pad of celite, the celite was washed well with ethanol, and the resulting bright yellow solution was concentrated *in vacuo*. Compound 704, a minor product from the hydrogenolysis reaction, was purified *via* HPLC (41 x 300 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient 0-50% B over 60 minutes, flow: 25 mL/min, retention time = 40.4 minutes).

The purified fractions were concentrated and lyophilized from water to give Compound 704 as a yellow fluffy solid in 6% (13.6 mg) purified yield. IR (KBr): 1716, 1698, 1682, 1651, 1636, 1609, 1542, 1509, 1473, 1458, 1428, 1385, 1365, 1278, 1237, 1202 cm^{-1}. EA (calculated for $C_{29}H_{28}N_2O_2$ • 2.0 $C_2HF_3O_2$ • 2.0 H_2O): C, 47.83; H, 4.14; N, 3.38. Found: C, 47.74; H, 3.97; N, 3.50.

Anti-4-[4-(2-Ethoxycarbonyl-6-hydroxybenzoyl-3,5-dihydroxybenzoyloxyl]-3-(4-hydroxybenzamido)pyrrolidine trifluoroacetic acid salt (COMPOUND 706)



705

706

To a stirred solution of aldehyde (1.62 mmol, 1.0 g) in acetonitrile (CH_3CN, 200 mL) at room temperature (nitrogen atmosphere) was added an aqueous solution of sulfamic acid (H_2NSO_3H, 2.11 mmol, 205 mg/10 mL water) in one portion. After stirring the reaction mixture for 5 minutes at room temperature, an aqueous solution of sodium chlorite ($NaClO_2$, tech., 80 %, 2.60 mmol, 235 mg/10 mL water) was added dropwise *via* an addition funnel. The reaction mixture was stirred for an additional 30 minutes under the same

conditions (Note 1: reaction was monitored by TLC), diluted with water (50 mL), and stirred for 10 minutes. The CH_3CN layer was removed *in vacuo* and the aqueous layer extracted with ethyl acetate (3 x 75 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. Benzophenone acid was purified *via* flash column chromatography and isolated (660 mg) in 65% purified yield as a white solid.

To a stirred solution of benzophenone acid produced from the previous reaction (1.03 mmol, 650 mg) in acetone (50 mL) under a nitrogen atmosphere was added potassium carbonate (5.14 mmol, 711 mg), and iodoethane (5.14 mmol, 800 mg), respectively, and in one portion. The reaction mixture was stirred at room temperature for 18 hours and concentrated under vacuum. The crude yellow solid was partitioned between chloroform (200 mL) and water (50 mL), and the organic layer was washed with saturated sodium bicarbonate solution, brine, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure. The resultant ethyl ester was isolated (560 mg) in 86% yield as a light yellow solid and used without purification (one spot by TLC, R_F 0.78 (2:1-hexane:ethyl acetate)).

t-Butyl ester (the ethyl ester from the previous reaction) (0.15 mmol, 100 mg) was dissolved in 1 mL of freshly distilled quinoline and placed into a flame-dried, 5 mL round-bottomed flask under a nitrogen atmosphere. The reaction flask was placed into a preheated oil bath (205 °C) and the solution stirred at 200-206 °C for 2.25 hours (reaction was carefully monitored by TLC). The dark brown solution was allowed to cool to room temperature, diluted with ether (Et_2O, 100 mL), washed with 10% HCl solution (3 x 25 mL), brine (25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting crude reaction mixture was purified *via* flash column chromatography and the benzophenone acid was isolated (480 mg) in 48% yield as a yellow solid.

COMPOUND 705

To a chilled (ice/water bath) and stirred solution of benzophenone acid produced in the previous reaction (0.40 mmol, 240 mg) in methylene chloride (5 mL) under a nitrogen atmosphere was added oxalyl chloride ($(COCl)_2$, 0.60 mmol, 77 mg), and N,N-dimethylformamide (DMF, catalytic, 1 drop), and the red-brown solution was stirred under the same conditions for 60 minutes. The resulting acid chloride was then concentrated *in vacuo* and stored at reduced pressure until needed. In a separate flask, pyrrolidinyl/alcohol (0.48 mmol, 215 mg) was dissolved in methylene chloride (5 mL) and stirred at room temperature under a nitrogen atmosphere. Triethylamine (Et_3N, 1.00 mmol, 102 mg) and 4-dimethyl aminopyridine (DMAP, catalytic, ≈ 2 mg) were added. A solution of the acid chloride (see above) in methylene chloride (5 mL) was added in one portion and the resulting red-brown solution was stirred at room temperature overnight (15-18 hours). The now deep-red solution was transferred to a separatory funnel, diluted with methylene chloride (100 mL), washed with saturated sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting red-brown foam was chromatographed on a silica column (6:1 to 3:1-hexane:ethyl acetate gradient), and perbenzylated intermediate Compound 705 was isolated (270 mg, 65 % yield, purified) as a yellow solid.

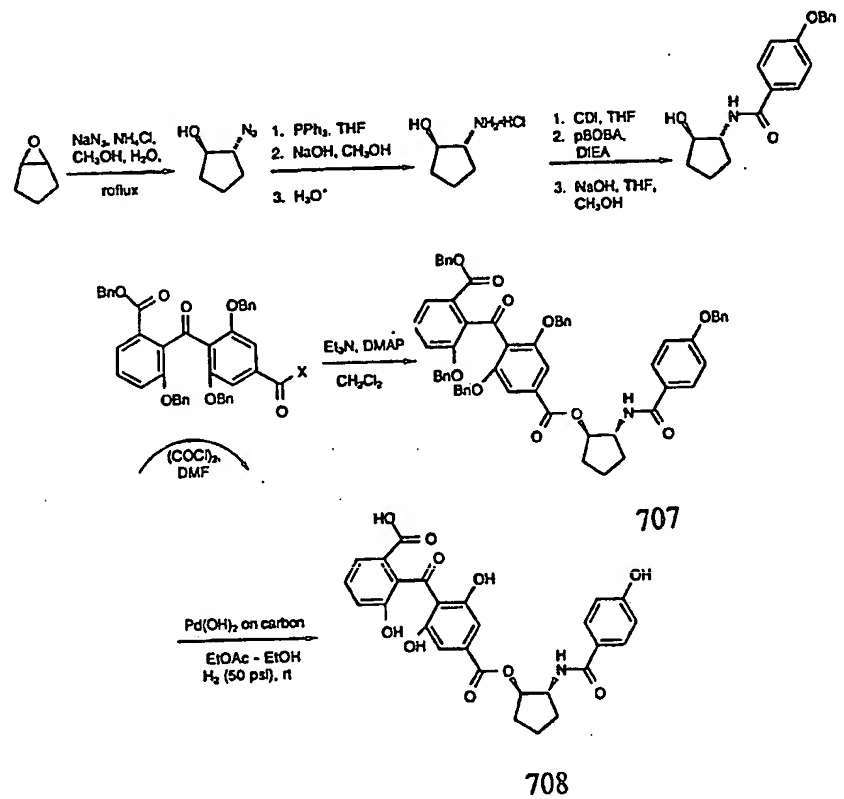
COMPOUND 706

Perbenzylated intermediate Compound 705 (0.24 mmol, 250 mg) was dissolved in ethanol (20 mL) and placed in a Parr shaker bottle. Pearlman's catalyst ($Pd(OH)_2$ on carbon, 20% palladium by weight, 50-75 mg) and trifluoroacetic acid (TFA, 2 drops) were added, and the mixture was shaken on the Parr hydrogenator at 50 psi of hydrogen atmosphere for 3 hours at room temperature (reaction monitored by TLC). The reaction mixture was diluted with ethanol (50 mL) and filtered over a pad of celite, the celite was washed well with ethanol, and

the resulting bright yellow solution was concentrated *in vacuo*. Compound 706 was purified *via* HPLC (41 x 300 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient 0-100% B over 60 minutes, flow: 25 mL/min). The purified fractions were concentrated and lyophilized from water to give 98.1 mg (75% yield, purified) of the title compound as a yellow fluffy solid. IR (KBr): 1723, 1676, 1606, 1427, 1371, 1300, 1229, 1201 cm^{-1}; EA (calculated for $C_{28}H_{26}N_2O_{10} \cdot 1.2C_2HF_3O_2 \cdot 2.0H_2O$): C, 50.48; H, 4.35; N, 3.87. Found: C, 50.28; H, 4.22; N, 3.76. MS (m/e, low resolution FAB): $[M + H]^+ = 551$.

***Anti*-1-[4-(2-Hydroxycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-2-(4-hydroxybenzamido)cyclopentane**

(COMPOUND 708)



To a 500 mL round bottomed flask containing methanol (200 mL) and water (50 mL) was added cyclopenteneoxide (59.5 mmol, 5.0 g), sodium azide (357.1 mmol, 23.2 g), and ammonium chloride (178.6 mmol, 9.6 g), respectively, and the clear solution was heated at reflux for 18 hours. (sodium azide may explode when heated, therefore, a blast shield should be used). The reaction mixture was allowed to cool to room temperature and the solvent evaporated *in vacuo* (use low heat when evaporating solvent).

The aqueous solution was diluted with 0.5 N NaOH (50 mL) and extracted with chloroform (3 x 100 mL). The chloroform solution was then washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The resultant azide (5.3 g) was isolated in 70% yield as a light yellow oil and used without purification (this compound may be fairly volatile, do not leave on vacuum pump).

To the azide solution of the previous reaction (7.9 mmol, 1.0 g) in tetrahydrofuran (THF, 100 mL) under nitrogen atmosphere was added triphenylphosphine (7.7 mmol, 2.3 g) and the clear solution stirred for 18 hours at room temperature. The solvent was then evaporated, and the viscous oil dissolved in methanol (50 mL). Sodium hydroxide solution (0.5 N, 20 mL) was added and the mixture stirred at room temperature for 36 hours, after which the solvent was evaporated *in vacuo*, (this product is volatile, use no heat), acidified to pH $\leq$ 3, and the aqueous layer washed with chloroform (100 mL). The crude hydrochloride salt was isolated as an off white solid after lyophilization of water, and used without purification. (the resultant amine hydrochloride was isolated as a mixture with the inorganic salt formed during the synthesis).

To a solution of 1,1'-carbonyldiimidazole (CDI, 12.6 mmol, 2.0 g) in methylene chloride (50 mL) was added 4-benzyloxybenzoic acid (pBOBA, 12.6 mmol, 2.9 g), and the mixture was stirred for 2 hours at room temperature under a nitrogen atmosphere. The imidazolide solution was added *via* cannula to a stirred white slurry of amine hydrochloride from the previous reaction (7.9 mmol, 1.1 g) and N,N-diisopropylethylamine (19.8 mmol, 2.6 g) in methylene chloride (50 mL) at room temperature under a nitrogen atmosphere and the mixture was stirred under these conditions for 18 hours. The solvent was evaporated *in vacuo* and the resulting tan solid was redissolved in THF/methanol (50 mL/50 mL), and allowed to react with 0.5 N NaOH solution (20 mL) for 2 hours at room temperature. The reaction mixture was

then concentrated and the aqueous layer was extracted with methylene chloride (3 x 50 mL), the combined organic layers washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to approximately 30 mL total volume (until the remaining solution became cloudy). The resultant hydroxyamide (945 mg, 38.5%) was triturated overnight by the slow addition of hexane (40-50 mL) and isolated as a white solid. No further purification was performed.

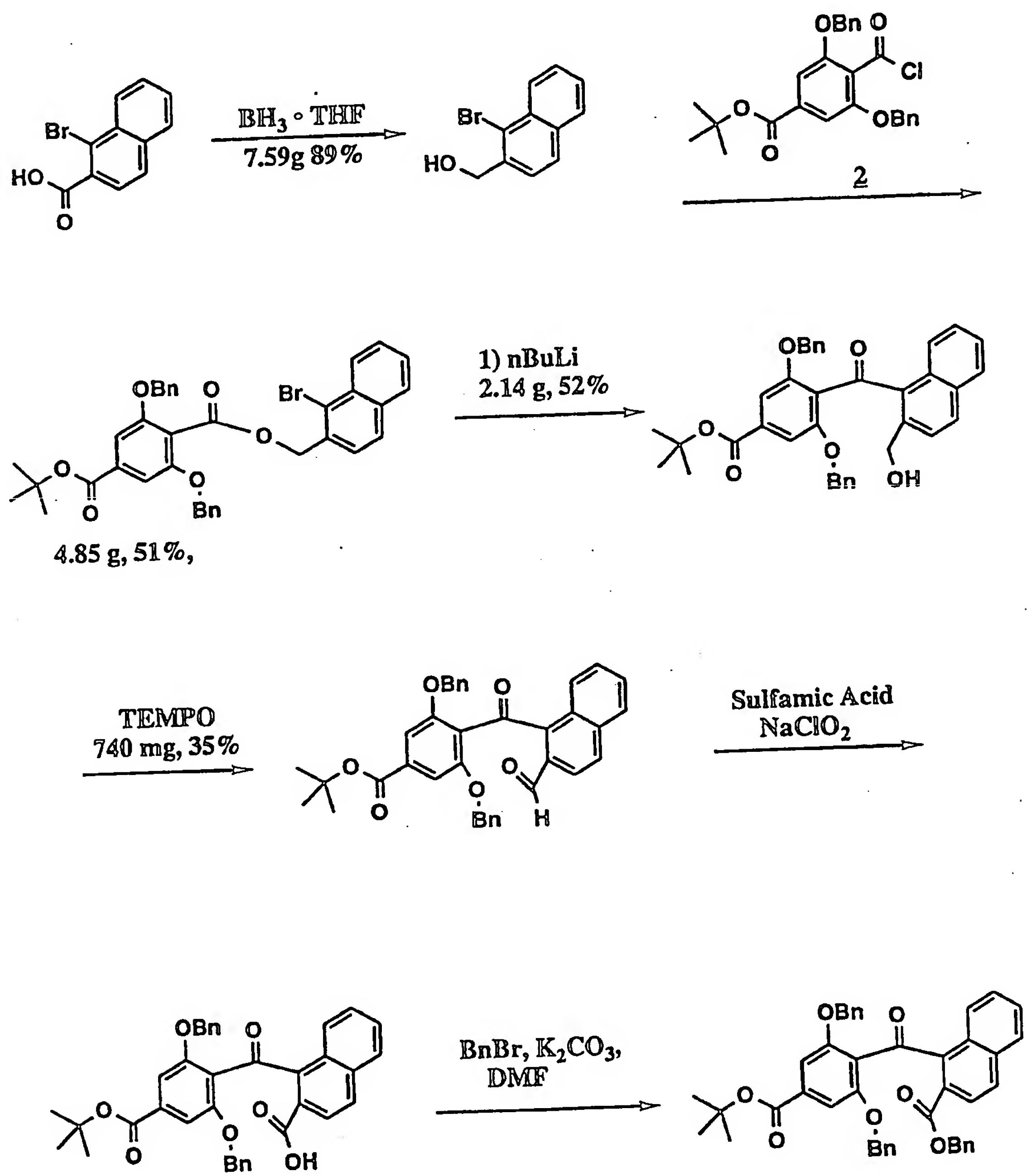
COMPOUND 707

To a chilled (ice/water bath) solution of benzophenone (0.45 mmol, 304 mg) in methylene chloride (5 mL) under a nitrogen atmosphere was added oxalyl chloride (0.67 mmol, 85 mg) and N,N-dimethylformamide (DMF, 1 drop). The resulting red-brown solution was stirred at 0-5°C for 2 hours and the resulting acid chloride was isolated as a red-brown solid after evaporation of the solvent *in vacuo* (solid was placed on vacuum pump for 30 minutes). In a separate flask, the hydroxyamide from the previous reaction (0.54 mmol, 167 mg) was dissolved in methylene chloride (5 mL) and chilled in an ice/water bath under a nitrogen atmosphere. Triethylamine (Et_3N, 1.12 mmol, 113 mg), 4-dimethylaminopyridine (DMAP, catalytic amount, tip of spatula), and a solution of the acid chloride (see above) in methylene chloride (5 mL) were added, respectively, to the reaction flask and the mixture was stirred at 0-5°C for 2 hours and then allowed to warm to room temperature overnight (15-18 hours). The deep red solution was diluted with methylene chloride (100 mL), washed with saturated sodium bicarbonate solution, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to produce a yellow-brown foam. Compound 707 was purified *via* flash column chromatography (4:1 hexane: ethyl acetate) and isolated (340 mg, 78% purified yield) as a light yellow-brown foamy solid.

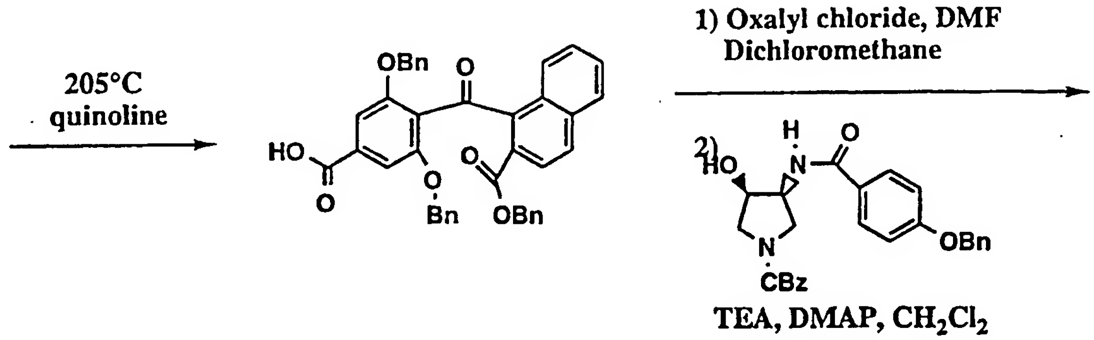
COMPOUND 708

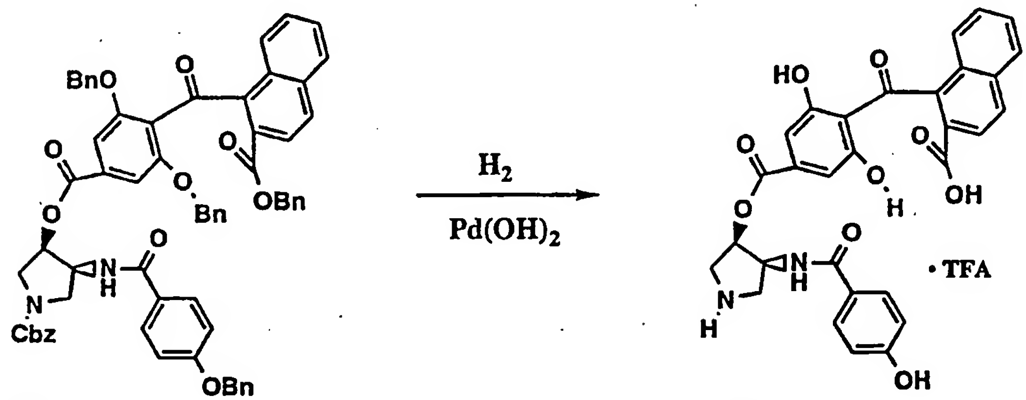
Perbenzylated intermediate Compound 707 (0.34 mmol, 330 mg) was dissolved in ethyl acetate (20 mL) and placed in a Parr shaker bottle. Ethanol (20 mL), and Pearlman's catalyst ($Pd(OH)_2$ on carbon, 20% palladium by weight, 150 mg) were then added, and the mixture was shaken on the Parr hydrogenator at 50 psi of hydrogen atmosphere for 3 hours at room temperature (reaction monitored by TLC). The reaction mixture was dissolved with ethanol (50 mL) and filtered over a pad of celite, the celite was washed well with ethanol, and the resulting bright yellow solution was concentrated *in vacuo*. Compound 708 was purified *via* HPLC (41 x 300 mm C18 reverse phase column, pump A: 5% acetonitrile in water + 0.1% trifluoroacetic acid; pump B: 100% acetonitrile; 0-100% pump B over 60 minutes, flow rate = 25 mL/min, retention time = 35.8 minutes). The purified fractions were concentrated and the water removed by lyophilization to give 168 mg (85% purified yield) of the title compound as a bright yellow solid. IR (KBr): 1703, 1633, 1606, 1507, 1425, 1373, 1245, 1200 cm^{-1}. EA (calculated for $C_{27}H_{23}NO_{10} \cdot 0.5C_2H_6O \cdot 2.0H_2O$): C, 57.93; H, 5.21; N, 2.41. Found: C, 57.67; H, 4.88; N, 2.62. MS (m/e, low resolution FAB): $[M + H]_+ = 522$.

(±)-*Anti*-3-(4-hydroxybenzamido)-4-[3,5-dihydroxy-4-[(2-hydroxycarbonyl)-1-naphthylcarbony]benzoyloxypyrrolidine, trifluor acetic acid salt (COMPOUND 710)



1-Bromo-2-naphthylmethanol





709 710

To 1-bromo-2-naphthoic acid (8.00 g, 31.9 mmol) in anhydrous THF (40 mL) under nitrogen at 0°C was added $BH_3 \cdot THF$ (74 ml, 0.74 mol, 1M in THF) dropwise over 0.5 h. The ice bath was removed and the mixture allowed to stir at room temperature for 5 h. The reaction was quenched with MeOH and the volatiles removed under reduced pressure. The mixture was diluted with ethyl acetate (750 mL) and washed with 2.5% $NaHCO_3$ (3 x 75 mL). The ethyl acetate layer was dried over $MgSO_4$, filtered and the volatiles removed under reduced pressure.

The crude product was purified by flash column chromatography (silica gel, chloroform) to provide a white solid (7.59 g, 89%). IR KBr (disc) cm^{-1} 3238, 3149, 3047, 2893, 2847, 1597, 1557, 1501, 1461, 1321, 1296, 1253, 1215,

1062, 966, 859, 807, 764, 736, 653. Anal. Calcd for $C_{11}H_9BrO_1$: C, 55.72; H, 3.83. Found: C, 55.92; H, 3.59.To a solution of *t*-butyl 3,5-dibenzyloxy-4-hydroxycarbonylbenzoate (6.38 g, 14.68 mmol) in anhydrous CH_2Cl_2 (60 mL) under nitrogen at 0°C was added oxalyl chloride (11 mL, 22.0 mmol) dropwise over 15 minutes followed by anhydrous DMF (5 drops). The mixture was allowed to stir while warming to room temperature over 3 h. The volatiles were removed and the resulting residue dried under vacuum at room temperature overnight. To 1-bromo-2-naphthylmethanol (3.83 g, 16.2 mmol) and DMAP (179 mg, 1.47 mmol) in anhydrous CH_2Cl_2 (60 mL) under nitrogen at 0°C was added triethylamine (TEA) (6.14 mL, 44 mmol) followed by the acid chloride in anhydrous CH_2Cl_2 (30 ml) over 0.5 h. The reaction mixture was allowed to stir while warming to room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (350 mL) and washed with water (125 mL) and brine (50 mL). The CH_2Cl_2 layer was dried over anhydrous magnesium sulfate, filtered, and the volatiles removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20: 1 hexane: ethyl acetate) to provide a white solid naphthyl methyl ester (4.85 g, 51%). IR KBr (disc) cm^{-1} 3064, 2975, 2932, 2874, 1738, 1715, 1583, 1559, 1505, 1456, 1423, 1369, 1328, 1248, 1162, 1119, 1079, 960, 863, 849, 812, 765, 739, 695, 668. Anal. Calcd for $C_{37}H_{33}O_6$: C, 68.00; H, 5.09. Found: C, 68.06; H, 5.07.

To a solution of the napthylmethyl ester (4.65 g, 7.11 mmol) in anhydrous THF (70 mL) under nitrogen at -78°C was added n-butyllithium (7.14 mL, 11.42 mmol, 1.6 M in hexanes) dropwise over 0.5 h, and the mixture was allowed to stir for 2.5 h at -78°C. The mixture was quenched by the dropwise addition of sat'd NH_4Cl (2 mL) at -78°C, and then allowed to stir continuously while the reaction material was allowed to warm to room temperature overnight. The reaction mixture was diluted with ethyl acetate (500 mL) and washed with water (200 mL). The ethyl acetate layer was dried over anhydrous $MgSO_4$, filtered and the volatiles removed under reduced pressure (no heat). The crude product

was purified by flash column chromatography (silica gel, 20: 1 hexane: ethyl acetate - 5:1 hexane: ethyl acetate) to provide a viscous oil of the naphthoyl alcohol (2.14 g, 52%).

To a solution of naphthoyl alcohol from the previous reaction (2.14 g, .72 mmol) in anhydrous CH_2Cl_2 (10 mL) was added distilled water (10 mL), KBr (66 mg, 0.558 mmol), $NaHCO_3$ (625 mg, 7.44 mmol), and TEMPO (6 mg, 0.0372 mmol). The reaction mixture was cooled to 0°C and NaOCl (6 mL, 4.09 mmol) was added dropwise over 10 minutes. Allowed to stir 2 h at 0°C. The reaction mixture was diluted with ether and washed with distilled water and brine. The ether layer was dried over anhydrous $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 10: 1 hexane:ethyl acetate - 3:1 hexane:ethyl acetate), which provided a white solid of the aldehyde (740 mg, 35%).

To a solution of the aldehyde from the previous reaction (720 g, 1.26 mmol) in acetonitrile (300 mL) was added a solution of sulfamic acid (171 mg, 1.76 mmol) in distilled water (6 mL) dropwise over 5 minutes at room temperature followed by the dropwise addition of a solution of $NaClO_2$ (207 mg, 1.83 mmol) in distilled water (6 mL) over 10 minutes.

The reaction mixture was allowed to stir for 1 h at room temperature, quenched with distilled water (30 mL), and allowed to stir for 10 minutes before removing the volatiles under reduced pressure. The residue was diluted with ethyl acetate (400 mL) and washed with distilled water (2 x 100 mL). The ethyl acetate layer was dried over anhydrous $MgSO_4$, filtered, and the volatiles were removed under reduced pressure, which provided a white solid of the corboxylic acid compound (730 mg, 99%).

To a solution of the carboxylic acid from the previous reaction (500 mg, 0.849 mmol) in anhydrous DMF under an atmosphere of nitrogen at room temperature was added anhydrous potassium carbonate (236 mg, 1.70 mmol) followed by the dropwise addition of benzyl bromide (121 μL, 1.02 mmol)

over 3 minutes. The reaction mixture was allowed to stir overnight at room termperature. The reaction mixture was diluted with ethyl acetate (125 mL) and washed with distilled water (30 mL), 1N HCl (3 x 30 mL), and brine (30 mL). The ethyl acetate layer was dried over anhydrous $MgSO_4$, filtered and the volatiles were removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20:1 hexane: ethyl acetate - 10:1 hexane ethyl acetate), which provided a white solid *t*-butyl ester compound (422 mg, 73%). IR KBr (disc) cm^{-1} 3064, 2975, 2933, 2871, 1715, 1669, 1600, 1571, 1545, 1503, 1459,. Anal. Calcd for $C_{44}H_{38}O_7$: C, 77.86; H, 5.64. Found: C, 77.76; H, 5.63.

A solution of the *t*-butyl ester from the previous reaction (345 mg, 0.508 mmol, JMD-467-119) in quinoline (3.5 mL) under an atmosphere of nitrogen was heated at 205°C for 3 h. The reaction mixture was diluted with ethyl acetate (125 mL) and washed with 1N HCl (4 x 30 mL). The ethyl acetate layer was dried over anhydrous $MgSO_4$, filtered and the volatiles were removed under reduced pressure. The product was chromatographed on a Dynanamax®-60 C18 column (41 mm ID X 30 cm length) using a linear gradient from 100C% A(0.1% TFA and 5% acetonitrile in water) to 100% B (pure acetonitrile) over 60 m at 25 mL/min. The product elutes in 61 minutes (in pure acetonitrile). After triturating the partially purified product with methanol, collection by suction filtration provided the phenyl carboxylic acid compound as a white solid (170 mg, 54%), mp 157-159°C. IR KBr (disc) cm^{-1} 3339, 3062, 3032, 2943, 2877, 1722, 1659, 1604, 1569, 1498, 1468, 1425, 1375, 1318, 1282, 1236, 1210, 1170, 1123, 1047, 955, 906, 867, 831, 767, 734, 698, 673. Anal. Calcd for $C_{40}H_{30}H_7 \cdot 0.25H_2O$: C, 76.60; H, 4.90. Found: C, 76.52; H, 4.76.

(±)-*Anti*-3-(4-benzyloxybenzamido)-4-{3,5-dibenzyloxy-4-[(2-benzyloxycarbonyl)-1-naphthylcarbcony]benzoyloxy}pyrrolidine (COMPOUND 709)

To a suspenision of the phenyl carboxylic acid from the previous reaction (158 mg, 0.254 mmol) in anhydrous

CH_2Cl_2 (10 mL) under an atmosphere of nitrogen at 0°C was added oxalyl chloride (190 μL, 0.381 mmol) dropwise over 10 minutes followed by anhydrous DMF (2 drops). The reaction mixture was allowed to stir while warming to room temperature over 1.5 h. The volatiles were removed under reduced pressure and the resulting residue was dried under full vacuum at room temperature overnight.

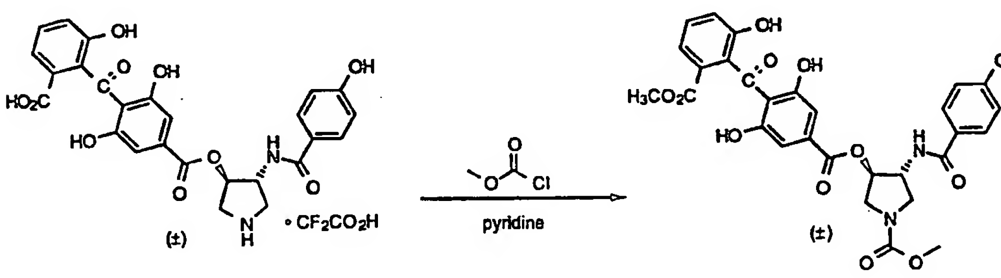
To a suspension of alcohol (150 mg, 0.764 mmol) and DMAP (3.1 mg, 0.0254 mmol) in anhydrous CH_2Cl_2 (4 mL) under an atmosphere of nitrogen at 0°C was added triethylamine (106 μL, 0.762 mmol) followed by a solution of the above generated acid chloride in anhydrous CH_2Cl_2 (5 ml) over 0.5 h. The reaction mixture was allowed to stir for 48 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with water (30 mL). The CH_2Cl_2 layer was dried over anhydrous magnesium sulfate, filtered, and the volatiles were removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, 3:1 hexane: ethyl acetate - 1:1 hexane: ethyl acetate) to provide a white solid of Compound 709 (212 mg, 79%), mp 86-89°C. IR KBr (disc) cm^{-1} 3033, 2942, 2882, 1713, 1656, 1607, 1569, 1540, 1501, 1459, 1423, 1369, 1324, 1279, 1247, 1178, 1111, 1050, 1024, 1005, 967, 906, 840, 806, 740, 695, 670. Anal. Calcd for $C_{66}H_{54}N_2O_{11}$ • $1H_2O$: C, 74.13; H, 5.28; N, 2.62. Found: C, 74.10; H, 5.03; N, 2.61.

(±)-*Anti*-3-(4-hydroxybenzamido)-4-{3,5-dihydroxy-4-[(2-hydroxycarbonyl)-1-naphthylcarbony]benzoyloxy}pyrrolidine, trifluoroacetic acid salt (COMPOUND 710)

To a solution of the (±)-*anti*-3-(4-benzyloxybenz amido)-4-{3,5-dibenzyloxy-4-[(2-benzyloxycarbonyl)-1-naphthylcarbonyl]benzoyloxy}pyrrolidine (208 mg, 0.198 mmol) in 10:1 ethyl acetate:ethanol (16 mL) under an atmosphere of nitrogen was added trifluoroacetic acid (15 μL, 0.198 mmol) followed by $Pd(OH)_2$ (51 mg, 25% by wt., 20% by wt. on C). The solution was placed under H_2 (1 atm) for 54 h. The reaction mixture was filtered and the volatiles were removed

from the filtrate under reduced pressure. The product was chromatographed on a Dynamax©-60 C18 column (21 mm ID X 30 cm length) using a linear gradient from 100% A (0.1% TFA and 5% acetonitrile in water) to 75% B (pure acetonitrile) over 60 m at 15 mL/min. The product elutes in 23 minutes. Removal of the volatiles under reduced pressure provided the Compound 710 as a yellow solid (60 mg, 41%), mp 192-195°C. IR KBr (disc) cm^{-1} 3431, 3302, 1681, 1637, 1559, 1542, 1509, 1458, 1427, 1393, 1369, 1225, 1203, 1145, 1109, 1074, 1048, 991, 927, 899, 870, 847, 799, 768, 724, 669, 619. FAB-MS m/z 557 $(M + H)^+$ Anal. Calcd for $C_{30}H_{24}N_2O_8 \cdot C_2HF_3O_2 \cdot 0.5H_2O$: C, 53.81; H, 3.80; N, 3.80. Found: C, 53.52; H, 3.74; N, 3.83.

(±)-*Trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-methoxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy]-N-methoxycarbonylpyrrolidine (COMPOUND 712)

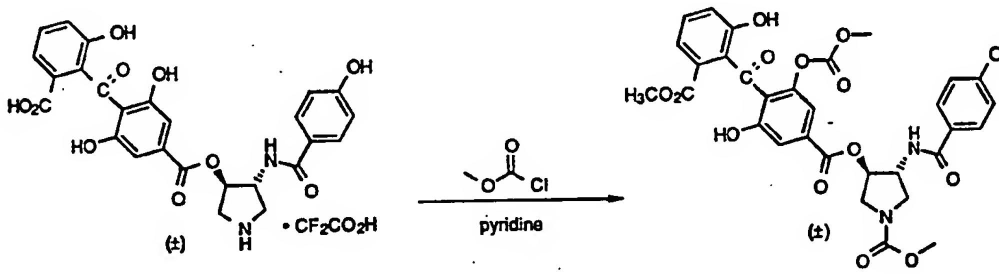


589 712

Anhydrous pyridine (1.5 mL) was added to a stirred mixture of (±)-*Trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-hydroxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidinium trifluoroacetate (Compound 589) (0.100 g, 0.157 mmol) and methyl chloroformate (97 µL, 1.26 mmol) at 0°C under N_2. The r sulting mixture was

stirred at 0°C for 2 h and was allowed to warm to room temperature and stir for 16 h. The solution was concentrated *in vacuo*. The residue was chromatographed on a 41x300 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0-50% B over 60 m; flow: 25 mL/m) affording the Compound 712 (7.8 mg, 8%) as a yellow gum. FABMS (m/z, $M^+ + 1$) 595.

(±)-*Trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-methoxycarbonylbenzoyl)-3-hydroxy-5-methoxycarbonyl benzoyloxy]-N-methoxycarbonylpyrrolidine (COMPOUND 713)

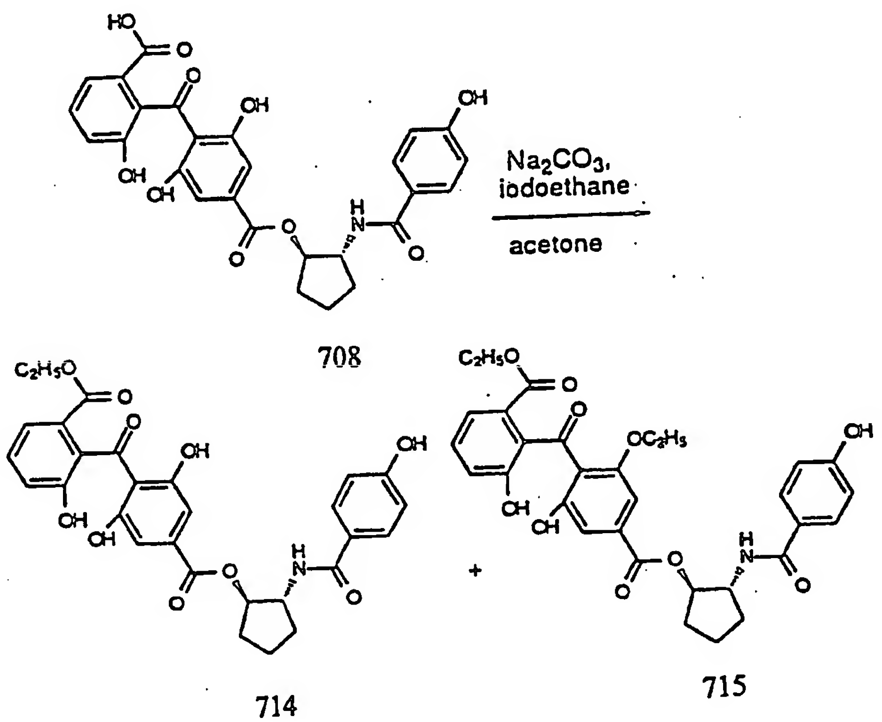


713

Anhydrous pyridine (1.5 mL) was added to a stirred mixture of (±)-*trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-hydroxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy] pyrrolidinium trifluoroacetate (COMPOUND 589) (0.100 g, 0.157 mmol) and methyl chloroformate (97 µL, 1.26 mmoL) at 0°C under N_2. The resulting mixture stirred at 0°C for 2 h and was allowed to warm to room temperature and stir for 16 h. The solution was then concentrated *in vacuo*. The residue was chromatographed on a 41 x 300 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0 - 50% B over 60 m; flow: 25 mL/m) affording the

Compound 713 (9.6 mg, 9 %) as a yellow gum. FABMS (m/z, M+ + 1) 653.

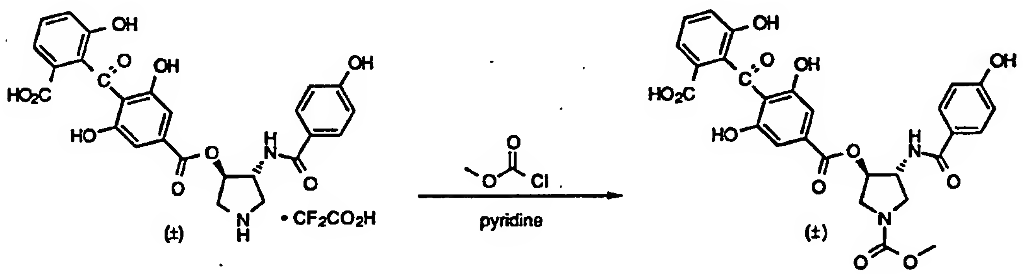
Anti-1-[4-(2-Ethoxycarbonyl-6-hydroxybenzoyl)-3-ethoxy-5-hydroxybenzoyloxy]-2-(4-hydroxybenzamido)cyclopentane (COMPOUND 715)



To a stirred solution of Compound 708 (0.15 mmol, 80 mg) in acetone (10 mL) was added anhydrous granular sodium carbonate (0.31 mmol, 33 mg) in one portion, and the reaction flask was purged with nitrogen at room temperature. Iodoethane (large excess, 10 mmol, 1.5 g) was added *via* syringe, and the deep yellow reaction mixture was stirred at room temperature for 24 hours. The solvent was evaporated *in vacuo* and the crude yellow solid was partitioned between ethyl acetate (100 mL) and water (25 mL). The organic layer was then washed with brine, dried over anhydrous sodium

sulfate, filtered, and concentrated under vacuum. Compound 715, a minor product of the alkylation reaction, was purified *via* HPLC (21 x 250 mm C18 reverse phase column, pump A: 5% acetonitrile in water + 0.1% trifluoroacetic acid; pump B: 100% acetonitrile; 0-100% pump B over 120 minutes, flow rate = 15 mL/min, retention time = 62.5 minutes). The purified fractions were concentrated and the water removed by lyophilization to give 5.4 mg (6% purified yield) of Compound 715 as a bright yellow solid. MS (m/e, low resolution FAB): $[M + H]^+ = 578$; $[M + Na]^+ = 600$.

(±)-*Trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-hydroxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy]-N-methoxycarbonyl pyrrolidine (COMPOUND 716)

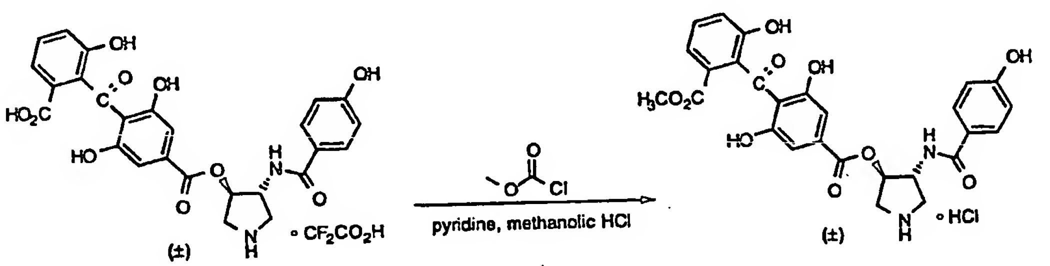


716

Anhydrous pyridine (0.25 mL) was added to a stirred mixture of (±)-*trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-hydroxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidinium trifluoroacetate (COMPOUND 589) (0.051 g, 0.080 mmol) and methyl chloroformate (12 µL, 0.160 mmol) at 0°C under N_2. The resulting mixture was

stirred at 0°C for 2 h and was then allowed to warm to room temperature and stir for 16 h. The solution was then concentrated *in vacuo*. The residue was chromatographed on a 41x300 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0 - 100% B over 60 m; flow: 25 mL/m) affording Compound 716 (4.2 mg, 9%) as a yellow gum. FABMS (m/z, M^+ + 1) 581.

(±)-*Trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-methoxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidinium hydrochloride (COMPOUND 717)



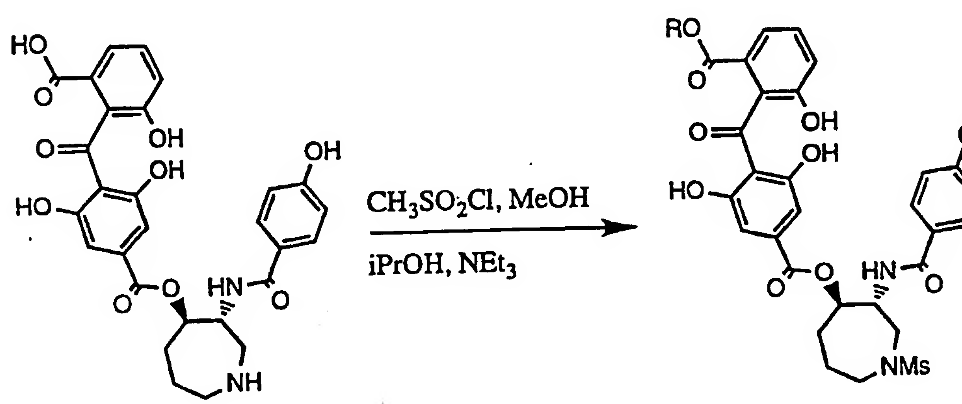
717

Anhydrous pyridine (0.1 mL) was added dropwise to stirred solution of (±)-*trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-hydroxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy] pyrrolidinium trifluoroacetate (COMPOUND 589) (0.025 g, 0.039 mmol) and methyl chloroformate (4.6 L, 0.059 mmoL) in methanolic HCl (0.25 mL) at 0°C under N_2. The resulting mixture was stirred at 0°C for 2 h and was then allowed to warm to room temperature and stir for 16 h. The solution was then concentrated *in vacuo*. The residue was chromatographed

on a 21x250 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0 - 100% B over 60 m; flow: 15 mL/m) affording the Compound 717 (0.9 mg, 3%) as a yellow gum after concentration from methanolic HCl. FABMS (m/z, $M^+ + 1$) 537.

Mesyl-Balanol and Mesyl-Balanol methyl ester (COMPOUND 718, COMPOUND 719)

COMPOUND 718, R = -H
COMPOUND 719, R = -CH3



718

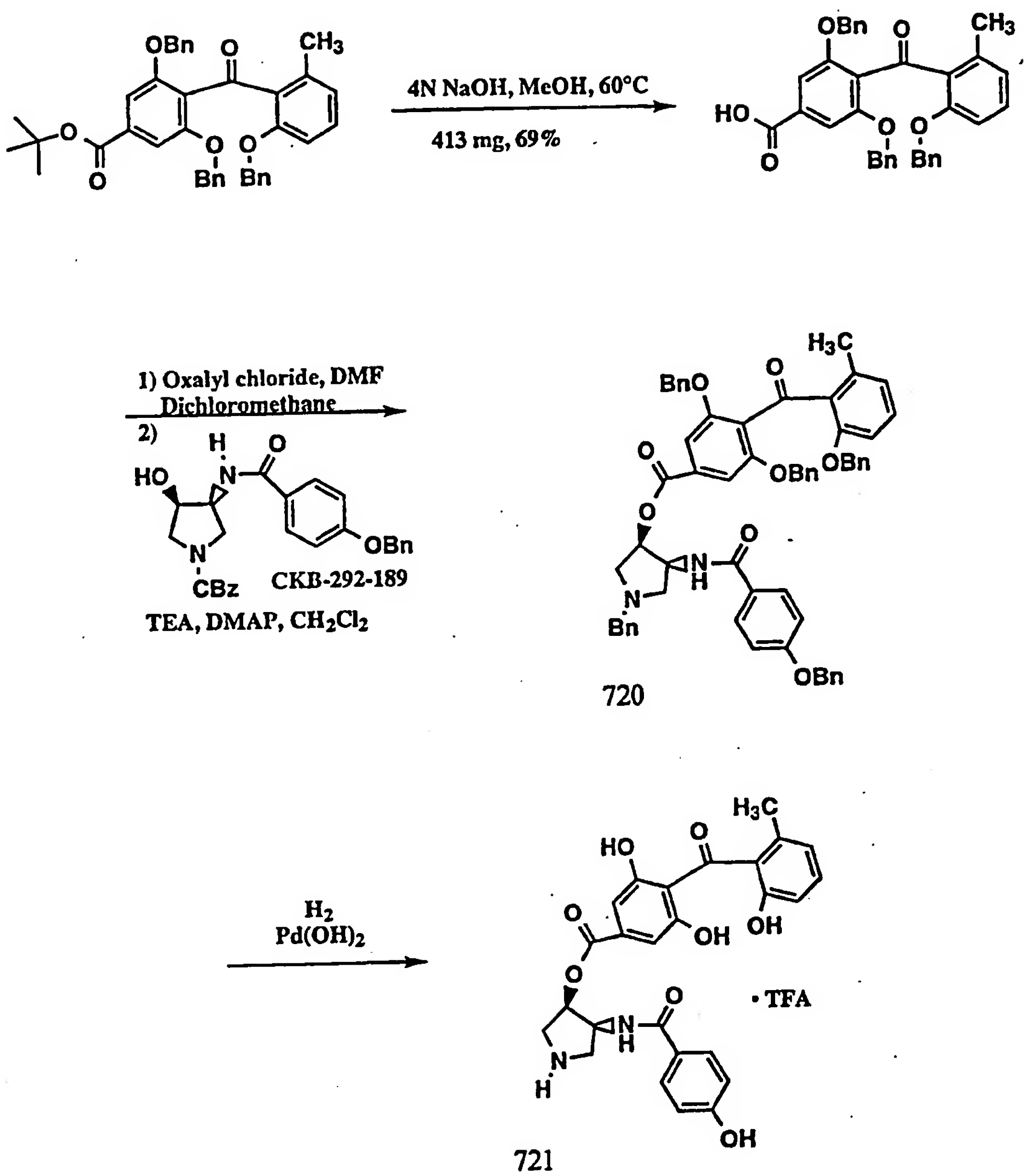
719

Synthetic (-)-balanol (30 mg, 43.9 µmol) was dissolved in isopropanol and methanol (≈ 5:1, 1.2 mL tot.), treated with triethyl amine (24 µL, 18 mg, 176 µmol) and methanesulphonyl chloride (10 µL, 15 mg, 132 µmol) and stirred for 16 h. TLC analysis indicated remaining starting material so additional aliquots of MsCl and NEt_3 were added until almost complete (3 times). The mixture was concentrated and the residue was chromatographed on a Dynamax -60 C_{18} column (21 X 250 mm) using a linear gradient

from 100% A (0.1% TFA and 5% acetonitrile in water) to 50% B (pure acetonitrile) over 60 m at 15 mL/min. The major product, which eluted in 40 min, was concentrated and scraped out to give synthetic mesylbalanol (COMPOUND 718) as a light yellow powder (9 mg). m.p. (dec) 180-190°C; ^{1}H-NMR (300 MHz, CD_3OD) δ 1.8-2.1 (4H, m's), 2.95 (3H, s), 3.3 (1H, m, hidden by H_2O), 2.5-2.65 (3H, m), 4.4 (1H, m), 5.26 (1H, m), 6.78 (2H, d, J = 8.7 Hz), 6.89 (2H, s), 7.00 (1H, d, J = 8 Hz), 7.26 (1H, t, J = 8 Hz), 7.48 (1H, d, J = 8 Hz), 7.64 (2H, d, J = 8.7 Hz), 8.1 (1H, d, J = 8.2 Hz, N<u>H</u>); IR (KBr): 3402, 1706, 1634, 1607, 1320, 1243 cm^{-1}; mass spectrum (FAB) m/z 651 (49%, M^+ + Na), 629 (100%, M^+ + 1). Anal. Calcd. for $C_{29}H_{28}N_2O_{12}S \circ 2.7\ H_2O \circ .15\ CF_3CO_2H$: C, 50.68; H, 4.87; N, 4.03; S, 4.62 Found: C, 56.64; H, 4.80; N, 4.03; S, 4.60.

The minor product, which eluted in 48 min, was concentrated and scraped out to give synthetic mesyl-balanol methyl ester (COMPOUND 719) as a light yellow powder (2.5 mg). m.p. (dec) 160-180°C; ^{1}H-NMR (300 MHz, CD_3OD) δ 1.85-2.15 (4H, m's), 2.95 (3H, s), 3.3 (1H, m, hidden by H_2O), 2.5-2.65 (3H, m), 3.67 (3H, s), 4.4 (1H, m), 5.26 (1H, m), 6.78 (2H, d, J = 8.7 Hz), 6.90 (2H, s), 7.03 (1H, d, J = 8.2 Hz), 7.28 (1H, t, J = 8.2 Hz), 7.46 (1H, d, J = 8.2 Hz), 7.64 (2H, d, J = 8.7 Hz); IR (KBr): 3436, 1709, 1633, 1608, 1303, 1240 cm^{-1}; mass spectrum (FAB) m/z 665 (70%, M^+ + Na), 643 (100%, M^+ + 1). Anal. Calcd. for $C_{30}H_{30}N_2O_{12}S \circ 2.7\ H_2O \circ .15\ CF_3CO_2H$: C, 50.39; H, 5.05; N, 3.85; S, 4.41 Found: C, 50.02; H, 4.68; N, 3.92; S, 4.59.

COMPOUND 721



3,5-dib nzyloxy-4-(2-benzyloxy-6-methyl)phenylcarbonylb nzoic acid

To a solution of the *t*-butyl 3,5-dibenzyloxy-4-(2-benzyloxy-6-methyl)phenylcarbonylbenzoate (685 mg, 1.11 mmol) in methanol (50 mL) was added 4N NaOH (5 mL) and the mixture was heated at 60°C overnight. After cooling to room temperature the reaction mixture was acidified with 1N HCl. The reaction mixture was diluted with ethyl acetate (250 mL) and washed with brine (30 mL). The ethyl acetate layer was dried over anhydrous $MgSO_4$, filtered and the volatiles were removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, chloroform - 3% methanol/chloroform) which provided the title compound as a white solid (413 mg, 69%), mp 63-66°C. IR KBr (disc) cm^{-1} 3446, 3183, 3033, 2943, 2873, 1732, 1685, 1653, 1578, 1541, 1521, 1492, 1457, 1423, 1376, 1315, 1258, 1218, 1114, 1024, 968, 906, 863, 834, 736, 698, 649. Anal. Calcd for $C_{36}H_{30}O_6$: C, 77.40; H, 5.41. Found: C, 77.75; H, 5.40.

(±)-*Anti*-3-(4-benzyloxybenzamido)-4-[(3,5-dibenzyloxy)-4-(2-benzyloxy-6-methyl)benzoyl]benzoyloxy-N-benzylpyrrolidine (COMPOUND 720)

To a suspension of the 3,5-dibenzyloxy-4-(2-benzyloxy-6-methyl)phenylcarbonylbenzoic acid (336 mg, 0.602 mmol) in anhydrous CH_2Cl_2 (7 mL) under an atmosphere of nitrogen at 0°C was added a solution of oxalyl chloride in CH_2Cl_2 (2.10 mL, 4.20 mmol) dropwise over 10 minutes followed by anhydrous DMF (2 drops). The reaction mixture was allowed to stir while warming to room temperature over 4 h. The volatiles were removed under reduced pressure and the resulting residue was dried under vacuum at room temperature overnight.

To a suspension of pyrrolidinyl alcohol (269 mg, 0.602 mmol) and DMAP (7 mg, 0.0602 mmol) in anhydrous CH_2Cl_2 (7 mL) und r an atmosphere of nitrogen at 0°C was added triethylamine (252 μL, 1.81 mmol) followed by a solution of the above generated acid chloride in anhydrous CH_2Cl_2 (8 ml)

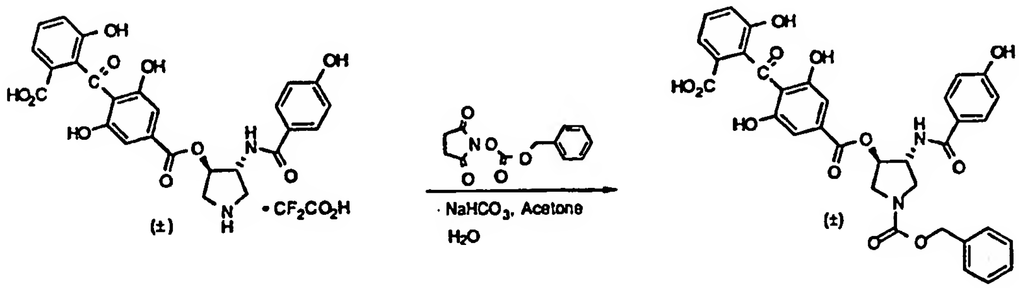
over 0.5 h. The reaction mixture was allowed to stir while warming to room temperature ov rnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with brine (230 mL). The CH_2Cl_2 layer was dried over anhydrous magnesium sulfate, filtered, and the volatiles were removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, 4:1 hexane:ethyl acetate - 1:1 hexane:ethyl acetate) to provide a the title compound as a white solid (371 mg, 62%), mp 79-83°C. IR KBr (disc) cm^{-1} 3395, 3064, 3032, 2947, 2882, 1708, 1684, 1660, 1605, 1582, 1538, 1501, 1455, 1422, 1370, 1324, 1226, 1179, 1108, 1014, 968, 908, 861, 844, 762, 738, 696. Anal. Calcd for $C_{62}H_{54}N_2O_{10}$: C, 74.44; H, 5.51; N, 2.84. Found: C, 75.13; H, 5.56; N, 2.83.

(±)-*Anti*-3-(4-hydroxybenzamido)-4-[(3,5-dihydroxy)-4-(2-methyl-6-hydroxy)benzoyl]benzoyloxypyrrolidine, trifluoroacetic acid salt (COMPOUND 721)

To a solution of (±)-*anti*-3-(4-benzyloxybenzamido)-4-[(3,5-dibenzyloxy)-4-(2-benzyloxy-6-methyl)benzoyl] benzoyloxy-N-benzylpyrrolidine (361 mg, 0.366 mmol) in 10:1 ethyl acetate:ethanol (40 mL) under an atmosphere of nitrogen was added trifluoroacetic acid (40 µL, 0.519 mmol) followed by $Pd(OH)_2$ (200 mg, 55% by wt., 20% by wt. on C). The solution was placed under H_2 (1 atm) overnight. The reaction mixture was filtered and the volatiles were removed from the filtrate under reduced pressure. The product was chromatographed on a Dynamax®-60 C18 column (41 mm ID X 30 cm length) using a linear gradient from 25% A (0.1% TFA and 5% acetonitrile in water) to 100% B (pure acetonitrile) over 60 m at 25 mL/min. The product elutes in 18 minutes. Removal of the volatiles under reduced pressure provided Compound 721 as a yellow solid (123 mg, 50%), mp 162-164°C. IR KBr (disc) cm^{-1} 3367, 3206, 2796, 1784, 1728, 1676, 1610, 1545, 1509, 1479, 1427, 1361, 1277, 1223, 1204, 1178, 1143, 1101, 1056, 1026, 988, 902, 849, 801, 766, 722, 643, 601. FAB-MS m/z 493

$(M + H)^+$ Anal. Calcd for $C_{26}H_{24}N_2O_8 \cdot 1.5\ C_2HF_3O_2 \cdot 0.5\ H_2O$: C, 51.79; H, 3.97; N, 4.17. Found: C, 51.59; H, 4.13; N, 4.25.

(±)-*Trans*-3-(4-hydroxybenzamido)-4[4(2-hydroxy-6-hydr xycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy]-N-benzyloxycarbonylpyrr lidine (COMPOUND 722)

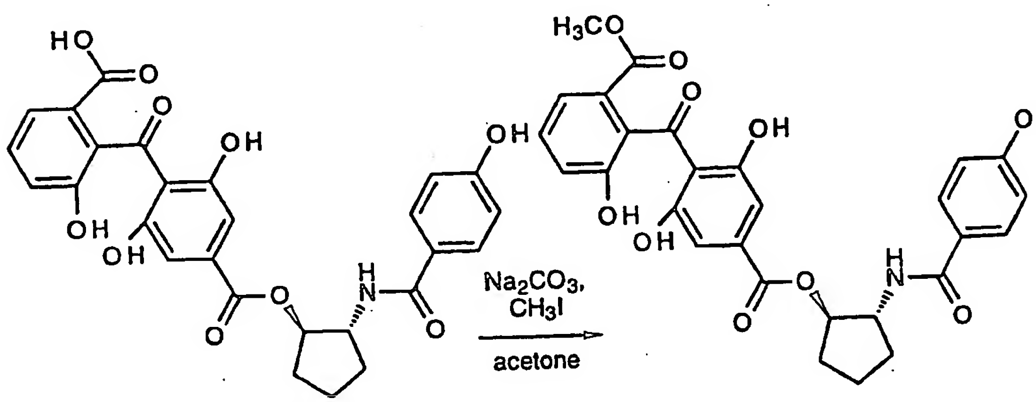


589 722

Benzyl succinimidyl carbonate (0.285 g, 1.14 mmoL) was added to stirred solution of $NaHCO_3$ (0.192 g, 2.28 mmoL) and (±)-*trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-hydroxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidinium trifluoroacetate (0.728 g, 1.14 mmoL) in 1:1 acetone/H_2O (30 mL) at room temperature. The resulting mixture stirred at room temperature for 16 h and was then concentrated *in vacuo*. The residue was chromatographed on a 41x300 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0-100% B over 60 m; flow: 25 mL/m) affording the Compound 722 (0.600 g, 80%) as a yellow solid. m.p.>185°C (dec.) Anal. Calcd. for $C_{34}H_{28}N_2O_{12}$ • 1.5 H_2O:

C, 61.35; H, 4.39; N, 4.21. Found C, 61.15; H, 4.62; N, 3.89.

(±)Anti-1-[4-(2-Methoxycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-2-(4-hydroxybenzamido)-cyclopentane (COMPOUND 723)

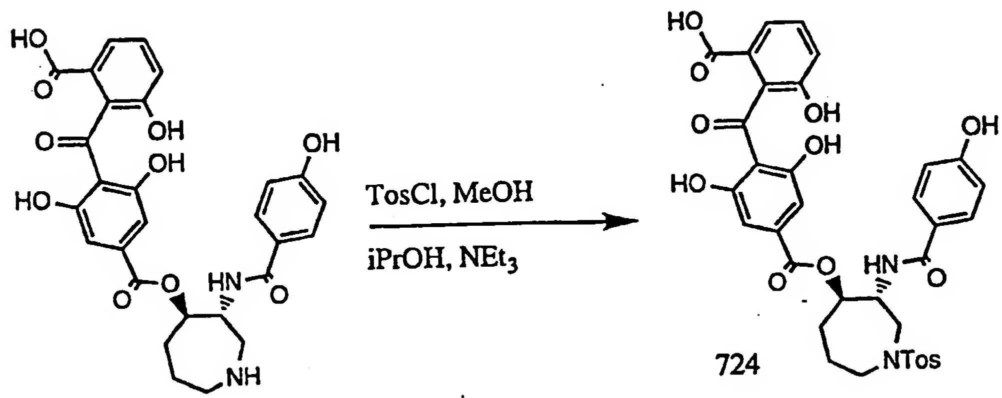


723

To a stirred solution of Compound 708 (0.48 mmol, 250 mg) in acetone (10 mL) was added anhydrous granular sodium carbonate (0.72 mmol, 77 mg) in one portion, and the reaction flask was purged with nitrogen at room temperature. Iodomethane (2.40 mmol, 340 mg) was added *via* syringe, and the deep yellow reaction mixture was stirred at room temperature for 48 hours. The solvent was evaporated *in vacuo* and the crude yellow solid was partitioned between ethyl acetate (100 mL) and water (25 mL). The organic layer was then washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Compound 723 was purified *via* HPLC (41 x 300 mm C18 reverse phase column, pump A: 5% acetonitrile in water + 0.1 % trifluoroacetic acid; pump B: 100% acetonitrile; 0-100% pump

B over 120 minutes, flow rate = 25 mL/min, retention time = 62.5 minutes). The purified fractions were concentrated and the water removed by lyophilization to give 30 mg (85% purified yield) of the title compound as a bright yellow solid. IR (KBr): 1704, 1635, 1607, 1506, 1425, 1366, 1301, 1240, 1174 cm^{-1}.

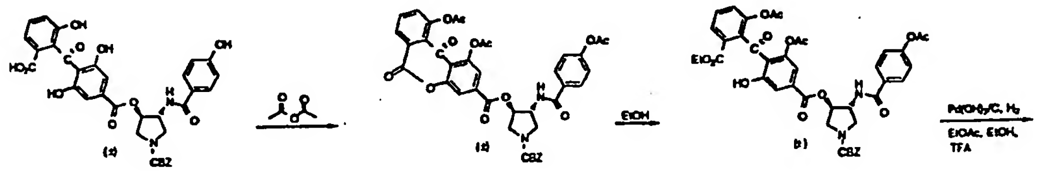
RACEMIC TOSYL-BALANOL (COMPOUND 724)



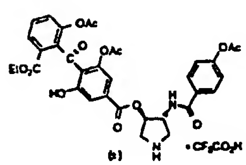
Synthetic racemic-balanol (400 mg, 586 μmol) was dissolved in methanol (10 mL), treated with triethyl amine (816 μL, 593 mg, 5.86 mmol) and toluenesulphonyl chloride (223 mg, 1.17 mmol) and stirred for 2 h. TLC analysis indicated some remaining starting material and product so the mixture was treated with water (1 mL) and stirred for 3 days. The mixture was concentrated and the residue was chromatographed on a Dynamax®-60C_{18} column (41 x 300 mm) using a linear gradient from 100% A (0.1% TFA and 5% acetonitrile in water) to 50% B (pure acetonitrile) over 60 m at 25 mL/min. The sample precipitated on the column and was eventually eluted with pure acetonitrile. A relatively clean fraction was concentrated, then triturated with water. The resulting yellow powder was filtered off and air dried to

give the product (146 mg, 35%) m.p. (dec) 160-180 °C; ^{1}H-NMR (300 MHz, CD^3OD) δ 1.8-2.0 (4N, m's), 2.38 (3H, s), 3.15-3.45 (4H, m), 4.27 (1H, m), 5.10 (1H, m), 6.76 (2H, d, J = 8.7 Nz), 6.76 (2H, s), 7.02 (1HN, d, J = 7.7 Nz), 7.26 (1H, t, J = 7.7 Nz), 7.40 (1H, d, J = 7.7 Hz), 7.40 (2H, d, J = 8.4 Hz), 7.64 (2N, d, J = 8.7 Nz), 7.68 (2H, d, J = 8.4 Hz), 8.2 (1H, d, J = 4.3 Hz, NH); IR (KBr): 3390, 1705, 1635, 1606, 1238 cm^{-1}; mass spectrum (FAB) m/z 705(100%, M^+ + 1). Anal. Calcd. for $C_{35}H_{32}N_2O_{12}S \circ 1.5H_2O$: C, 57.45; H, 4.82; N, 3.82; S, 4.38 Found: C, 57.48; H, 4.75; N, 3.70; S, 4.19.

(±)-*Trans*-3-(4-acetoxybenzamido)-4-[4-(2-acetoxy-6-ethoxycarbonylbenzoyl)-3-acetoxy-5-hydroxybenzoyl xy] pyrrolidinium trifluoroacetat



722 725



726

A solution of (±)-*trans*-3-(4-hydroxybenzamido)-4[4(2-hydroxy-6-hydroxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy]-N-benzyloxycarbonyl pyrrolidine (Compound 722) (0.100 g, 0.152 mmol) in acetic anhydride (4 mL) was heated to reflux for 15 min. The solution was then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in hot $CHCl_3$ and filtered from activated carbon. The filtrate was concentrated *in vacuo*, the residue triturated with Et_2O and the resulting white

solid filtered, affording the lactone compound (80 mg, 69%). FABMS (m/z, M^+ + 1) 765.

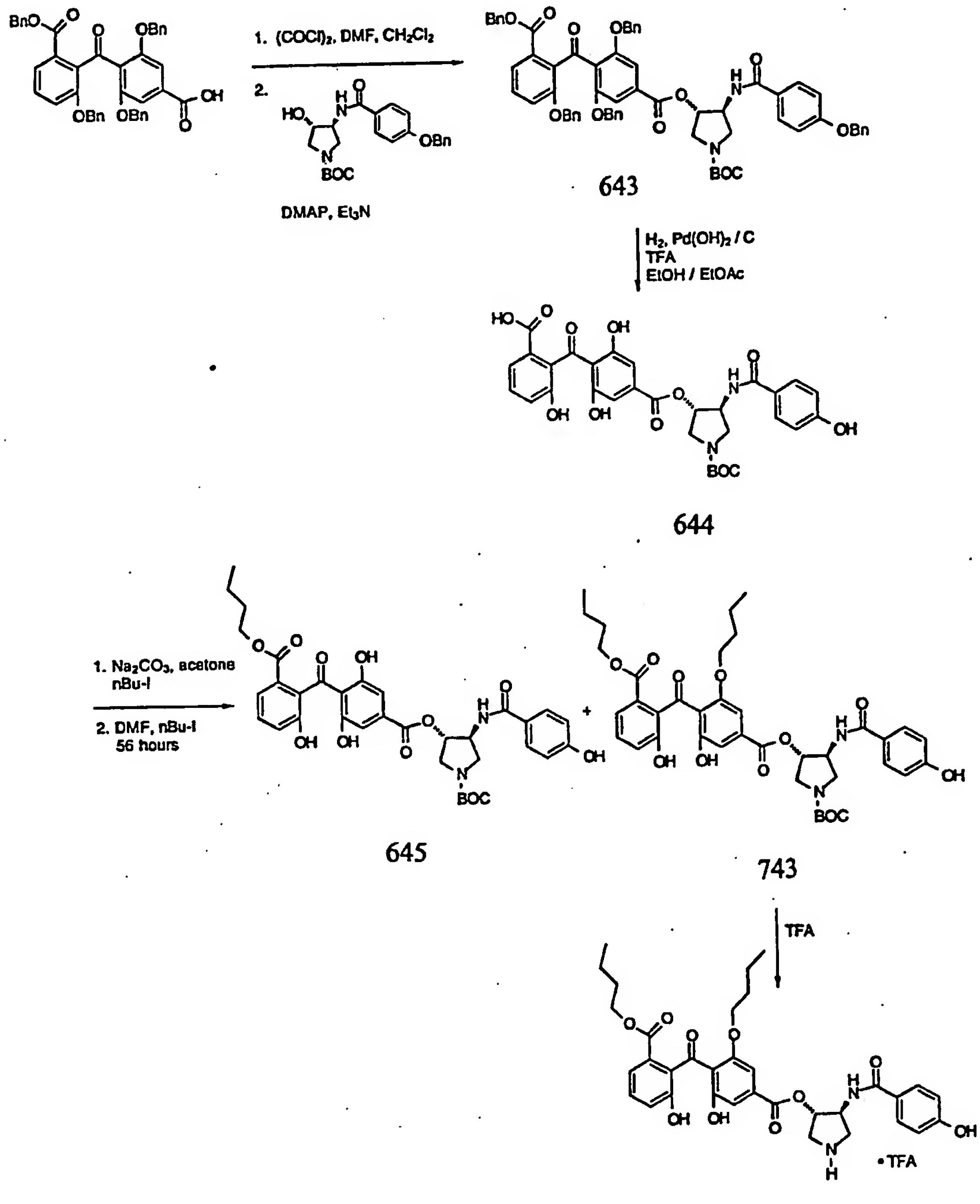
COMPOUND 725

A mixture of the lactone product from the previous reaction (20 mg, 0.026 mmol) in absolute ethanol (1.5 mL) became homogenous as it was heated to reflux for 1 h under N_2. The solution was cooled to 0°C and the unreacted starting material filtered (5 mg). The filtrate was concentrated affording a colorless oil (19 mg, > 100% based on unreacted starting material). The compound was used without further purification.

(±)-*Trans*-3-(4-acetoxybenzamido)-4[4-(2-acetoxy-6-ethoxycarbonylbenzoyl)-3-acetoxy-5-hydroxybenzoyloxy] pyrrolidinium trifluoroacetate (COMPOUND 726)

Moist palladium hydroxide on carbon (19 mg, 20 % Pd) was added to a solution of Compound 725 (0.019 g, ca.0.024 mmol) in EtOH (1.5 mL), EtOAc (1 mL) and TFA (0.25 mL). The mixture was stirred under 1 atm. of hydrogen for 40 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was chromatographed on a 21x250 mm C18 column (solvent A:95:5 water/acetonitrile 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0 - 100% B over 60 m; flow: 15 ml/min) affording Compound 726 (3.2 mg, ca. 17%) as a yellow solid. FABMS Calcd. for $C_{34}H_{32}N_2O_{13}$ (m/z, M^+ + 1): 676.1904; found 676.1992.

(±)-*Trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-butoxycarbonylbenzoyl)-3-butoxy-5-hydroxybenzoyl xy] pyrrolidine trifluoroacetic acid salt (COMPOUND 727)



643

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645

743

727

(±)-trans-N-t-but xycarbonyl-3-(4-benzyloxybenzamido)-4-[4-(2-benzyloxy-6-benzyloxycarbonylbenzoyl)-3,5-dibenzyloxy benzoyloxy]pyrrolidine (COMPOUND 643)

4-[4-(2-benzyloxy-6-benzyloxycarbonylbenzoyl)]-3,5-dibenzyloxybenzoic acid (1.47 mmol, 996 mg) and 15 mL anhydrous CH_2Cl_2 in a dry round-bottom flask were cooled in an ice/water bath under N_2. To this was added oxalyl chloride (2.87 mol, 0.25 mL) and 5 drops of DMF. This was allowed to stir for 2 hours while the bath melted. TLC (2:1 hexanes: EtOAc) indicated complete formation of the acid chloride. The solvent was removed *in vacuo*.

In a 200 mL dry round-bottom flask was added (±)-*trans*-N-t-butoxycarbonyl-3-(4-benzyloxybenzamido)-4-hydroxy pyrrolidine (1.26 mmol, 500 mg) in 12 mL anhydrous CH_2Cl_2 under N_2. To this was added triethylamine (3.6 mmol, 0.5 mL) and DMAP (150 mg). A solution of the acid chloride generated above in 10 mL anhydrous CH_2Cl_2 was added *via* cannula. This was allowed to stir under N_2 at room temperature overnight. The reaction mixture was then diluted with CH_2Cl_2, washed with sat. $NaHCO_3$, brine, then dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography using 5% acetone/CH_2Cl_2 as the eluent. Compound 643 (1.08 mmol, 1.15 g) was obtained in 86% yield.

(±)-*Trans*-N-t-butoxycarbonyl-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-carboxybenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine (COMPOUND 644)

To a 500 mL 3-neck round-bottom flask was added (±)-*trans*-N-t-butoxycarbonyl-3-(4-benzyloxybenzamido)-4-[4-(2-benzyloxy-6-benzyloxycarbonylbenzoyl)-3,5-dibenzyloxy benzoyloxy]pyrrolidine (Compound 643, 1.02 mmol, 1.08 g) in 17 mL EtOAc and 70 mL ethanol under N_2. To this was added trifluoroacetic acid (2.55 mmol, 0.20 mL) and $Pd(OH)_2/C$ (730 mg) followed immediately by introduction of H_2 at 1 atmosphere. After a reaction time of 3.5 hours, the reaction

was flushed with N_2 and filtered through Celite, rinsing with ethanol. Following concentration *in vacuo*, crude product (Compound 644, 644 mg) was obtained in quantitative yield. A small portion was purified *via* HPLC (21 x 250 mm C18 column, gradient %B = 0 to 50 over 60 min. where A = 0.1% TFA, 5% CH_3CN in water and B = CH_3CN, 15 mL/min. UV = 254 nm) for characterization and the remainder was used crude in subsequent reactions. m.p. 196°C (dec). IR (KBr) 3375(br), 2978, 1704, 1660, 1637, 1607, 1506, 1426, 1368, 1231 cm^{-1}. 1H NMR CD_3OD, δ 8.52 (d, 1H), 7.72 (d, 2H), 7.49 (d, 1H), 7.26 (t, 1H), 7.01 (d, 1H), 6.91 (s, 2H), 6.80 (d, 2H), 5.40 (m, 1H), 4.63 (m, 1H), 3.87 (m, 2H), 3.50 (m, 2H), 1.47 (s, 9H). LRMS (M + 1) cacld for $C_{31}H_{31}N_2O_{12}$ 623.2, found 623.2. Anal. Calcd for $C_{31}H_{30}N_2O_{12}$ • 1.5 H_2O: C, 57.317; H, 5.120; N, 4.312. Found: C, 57.26; H, 5.18; N, 4.47.

(±)-*Trans*-N-t-butoxycarbonyl-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-butoxycarbonylbenzoyl)-3-butoxy-5-hydroxy benzoyloxy]pyrrolidine (COMPOUND 743)

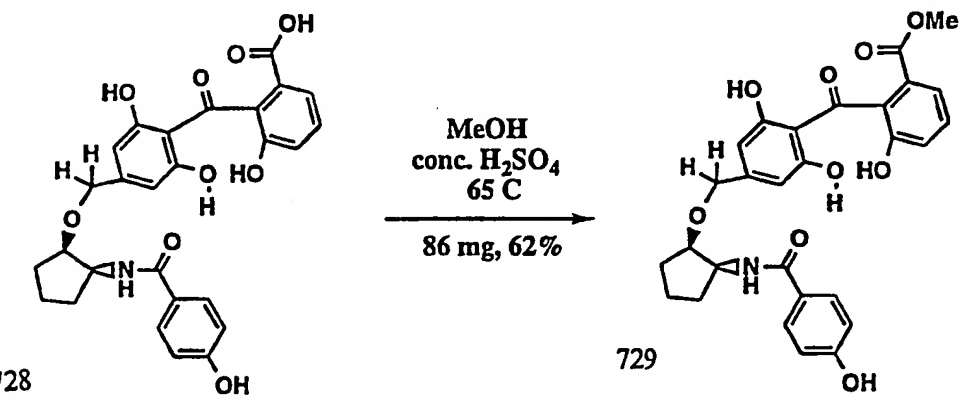
To a 25 mL round-bottom flask was added (±)-*trans*-N-t-butoxycarbonyl-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-carboxybenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine (Compound 644, 0.17 mmol, 104 mg) in 5 mL acetone. To this was added Na_2CO_3 (0.27 mmol, 29 mg) and 1-iodobutane (0.88 mmol, 0.1 mL). This was allowed to stir under N_2 for 18 hours at which time TLC (EtOAc) showed no reaction taking place. Next was added additional 1-iodobutane (1.7 mmol, 0.2 mL) and 2 mL DMF to increase solubility of the Na_2CO_3 The reaction stirred under N_2 for an additional 38 hours at which time the reaction mixture was diluted with EtOAc and washed with brine 4 times. The crude product was purified *via* flash column chromatography (eluent, 2:1 CH_2Cl_2: acetone to 1:1 CH_2Cl_2: MeOH) at which time 2 products were identified (COMPOUNDS 743 and 645). Further purification *via* HPLC (21 x 250 mm C18 column, gradient %B = 0 to 100 over 60 min. where A = 0.1% TFA, 5% CH_3CN in water and B = CH_3CN, 15 mL/min. UV = 254 nm)

was necessary to isolate (±)-*trans*-N-t-butoxycarbonyl-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-butoxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine (Compound 645, 517-88D, 20 mg, 36% yield) from (±)-*trans*-N-t-butoxycarbonyl-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-butoxycarbonylbenzoyl)-3-butoxy-5-hydroxybenzoyloxy]pyrrolidine (Compound 743, 32 mg, 25% yield).

(±)-*Trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-butoxycarbonylbenzoyl)-3-butoxy-5-hydroxybenzoyloxy] pyrrolidine trifluoroacetic acid salt (COMPOUND 727).

(±)-*Trans*-N-t-butoxycarbonyl-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-butoxycarbonylbenzoyl)-3-butoxy-5-hydroxybenzoyloxy]pyrrolidine (Compound 743, 0.044 mmol, 32 mg) was dissolved in 0.6 mL neat trifluoroacetic acid and allowed to stir at room temperature under N_2 for 50 minutes at which time TLC (75% CH_2Cl_2, 24% MeOH, 1% (10% aq.) NH_4OH) indicated the reaction was complete. This was diluted with toluene and concentrated *in vacuo* to yield crude product. Purification *via* HPLC (21 x 250 mm C18 column, gradient %B = 0 to 100 over 60 min. where A = 0.1% TFA, 5% CH_3CN in water and B = CH_3CN, 15 mL/min. UV = 254 nm) yielded (±)-*trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-butoxycarbonylbenzoyl)-3-butoxy-5-hydroxybenzoyloxy]pyrrolidine trifluoroacetic acid salt (Compound 727, 20 mg, 60% yield) as a yellow solid. m.p. 122-128°C (dec.). IR (KBr) 3393 (br), 2962, 1680, 1606, 1507, 1425, 1362, 1298, 1207 cm^{-1}. ^1H NMR, CD_3OD, δ 7.75 (d, 2H), 7.51 (d, 1H), 7.34 (t, 1H), 7.27 (d, 1H), 7.04 (d, 1H), 7.01 (s, 1H), 6.83 (d, 2H), 5.66 (m, 1H), 4.65 (m, 1H), 4.10 (t, 2H), 3.98 (dd, 1H), 3.86 (dd, 1H), 3.75 (t, 2H), 3.61 (m, 2H), 1.49 (m,2H), 1.27 (m, 2H), 1.00 (m, 4H), 0.83 (t, 3H), 0.75 (t, 3H). LRMS (M + 1) calcd for $C_{34}H_{39}N_2O_{10}$ 635.26, found 635.0. Anal. Calcd for $C_{34}H_{38}N_2O_{10} \circ C_2HF_3O_2 \circ H_2O$: C, 56.39; H, 5.39; N, 3.65. Found: C, 56.31; H, 5.16; N, 3.71.

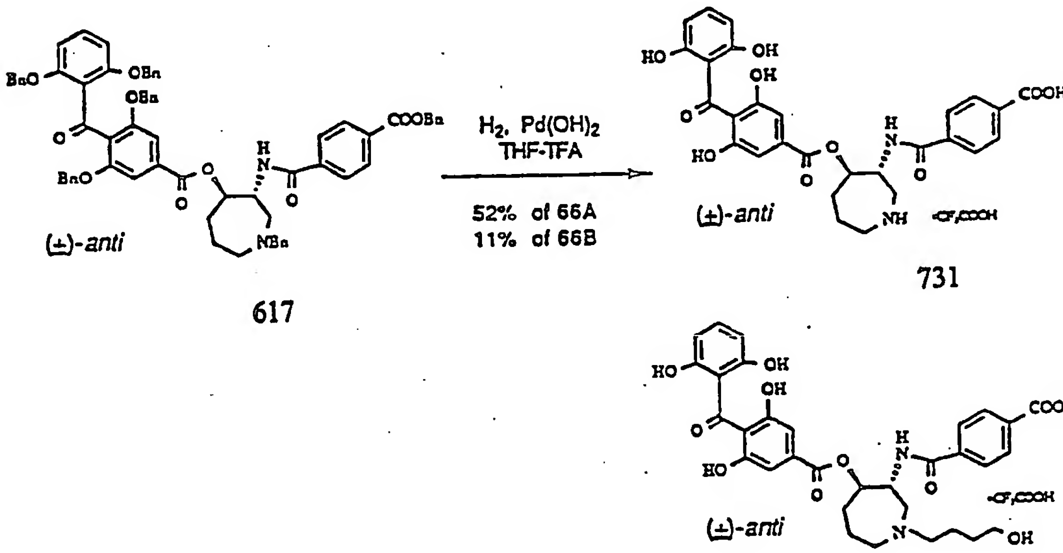
(±)-*Anti*-1-[4-(2-Methoxycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxybenzyloxy]-2-(4-hydroxybenzamido)cyclopentane (COMPOUND 729)



To a solution of (±)-anti-1-[4-(2-hydroxycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxybenzyloxy]-2-(4-hydroxybenz amido)cyclopentane (128 mg, 0.245 mmol, Compound 728) in anhydrous methanol (15 mL) was added conc. H_2SO_4 (5 drops) and the reaction mixture was heated at 65°C for 48 h. The volatiles were removed under reduced pressure. The crude residue was purified by prep. TLC (silica gel, developed 2 x 25:2 chloroform:methanol) which provided a yellow solid of Compound 728 (86 mg, 62%), mp 145-148°C. ^{13}C NMR (MeOH-d_4) δ 203.2 (s), 170.5 (s), 168.7 (s), 164.0 (s), 162.5 (s), 155.3 (s), 150.5 (s), 135.0 (s), 130.9 (d, 2C), 130.4 (d), 129.8 (s), 127.2 (s), 122.2 (d), 121.5 (d), 116.6 (d, 2C), 112.2 (s), 106.9 (d, 2C), 86.9 (d), 71.8 (t), 58.4 (d), 53.1 (q), 32.3 (t), 32.0 (t), 23.4 (t). IR KBr (disc) cm^{-1} 3381, 2954, 2876, 1706, 1636, 1606, 1543, 1505, 1463, 1433, 1371, 1300, 1253, 1203, 1175, 1106, 1062, 1012, 926, 847, 802, 761, 701.

FAB-MS m/z 522 $(M + H)^+$ Anal. Calcd for $C_{28}H_{27}NO_9$: C, 64.49; H, 5.22; N, 2.69. Found: C, 64.18; H, 5.14; N, 2.72.

(±)-*Trans*-3-(4-Carboxybenzamido)-4-[3,5-dihydroxy-4-(2,6-dihydroxy) phenylcarbonylbenzoyloxy-N-(4-hydroxybutyl) perhydroazepine trifluoroacetic acid salt (COMPOUND 730)



617

731

730

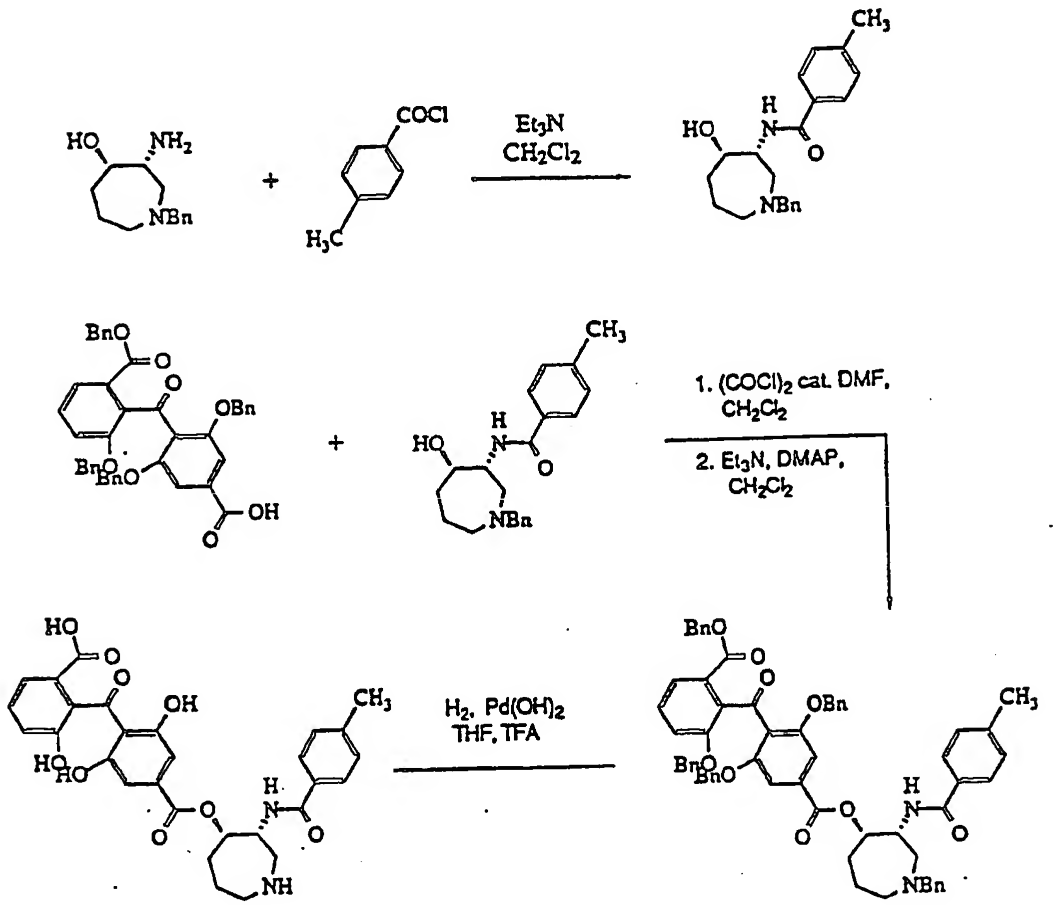
The synthesis of Compound 617 was reported in the preparation of Compound 536.

COMPOUND 730

Compound 617 (200 mg, 0.183 mmol) was dissolved in THF (20mL) and treated with few drops of TFA and 10% $Pd(OH)_2$ (120mg, 62 mol %). The mixture was subject to hydrogenolysis at 50 psi for 30 hr. THF was removed *in vacuo* and the residue taken into MeOH. The MeOH solution was concentrated after filtering through a pad of celite and chromatographed

on 41 x 300 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0-100% B over 60 min, flow: 25 mL/min). Fractions (one/min) 41-42 were evaporated and lyophilized to give yellow fluffy solids (Compound 731, 63.5mg, 52%). Fraction 44 gave a minor product (Compound 730, 15.0 mg, 11%). m.p. 160-164 (dec)°C; 1H NMR (CD_3OD) δ 8.07 (d, J = 8.3Hz, 2H, ArH), 7.84 (d, J = 8.1 Hz, 2H, ArH), 7.19 (t, 1H, ArM), 6.96 (s, 2H, ArH), 6.28 (d, J = 8.3Hz, 2H, ArH), 5.48 (m, 1H, C_4-H), 4.60 (m, 1H, C_3-H), 3.65 (m, 5H, CH_2), 2.40-1.60 (m, 8H); IR (KBr) cm^{-1} 3411, 1703, 1677, 1648, and 1626. Anal. Calc. for $C_{32}H_{34}N_2O_{11}$ • $3.0H_2O$ • 1.3TFA: C,50.38; H, 5.05; N, 3.40. Found: C, 50.16; H, 4.77; N, 3.85. LRFAB (M + 1): 623.

(+)-*Trans*-3-(4-Methylbenzamido)-4-[4-(2-carb xy-6-hydroxy) benz yl-3,5-dihydroxy]benzoyloxyperhydroazepine trifluoroacetice acid salt (COMPOUND 732)



732

733

To a solution of azepine (1.0 g, 4.54 mmol) and Et_3N (1.25 mL, 9.0 mmol) in anhydrous CH_2Cl_2 (10 mL) was slowly added toluoyl chloride (0.72 mL, 5.45 mmol) at room temperature. The mixture was stirred at room temp rature for 1 hr. Solvents were removed and the residue was

chromatographed using 2:1/Hexane:EtOAc to 4:3/EtOAc:hexane to yield a clear oil. Trituration of the oil in hexane gave white solids (689 mg, 45%).

COMPOUND 733

To a solution of benzophenone acid (235mg, 0.346mmol) in CH_2Cl_2 (3mL) was added cat. DMF and oxalyl chloride (2.0 M solution in CH_2Cl_2, 0.433mL, 0.865mmol) at room temperature. The mixture was stirred at room temperature for 2 hr. Solvents were removed and the acid chloride residue was taken into CH_2Cl_2 (5mL) after drying over the vacuum for 1hr.

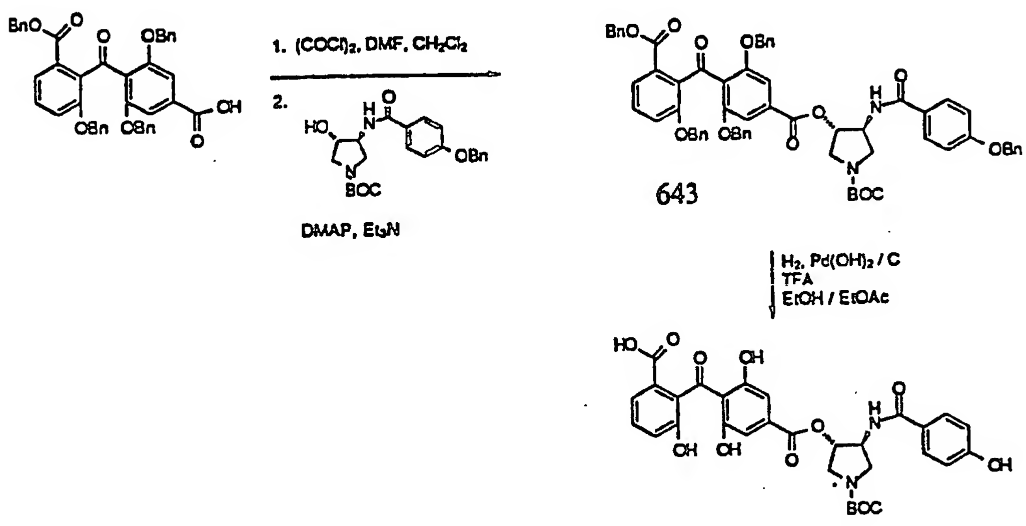
A solution of amidoalcohol (117.1 mg, 0.346 mmol), Et_3N (175.1 mg, 241 μL, 1.73 mmol) and DMAP (42.3 mg, 0.346 mmol) in CH_2Cl_2 (5 mL) was treated with the freshly made acid chloride-CH_2Cl_2 solution (5 mL) at 5°C. The reaction mixture was allowed to stir at room temperature for overnight and chromatographed on silica gel with 1:2/EtOAc:Hexane as an eluent to afford light yellow sticky solids (Compound 733, 241 mg, 70%).

COMPOUND 732

Compound 733 (227 mg, 0.227 mmol) was dissolved in THF-EtOH (5:1, 18 mL) and treated with TFA (cat.) followed by 10% $Pd(OH)_2$ (134 mg, 60 mol%). The mixture was subject to hydrogenolysis at 50 psi for 24 hr. Solvents were concentrated after filtering through a pad of celite, and the residue was dissolved in DMF (0.75 mL) and loaded onto HPLC; conditions: A-0.1%/TFA5%/CH_3CN/H_2O, B-100%CH_3CN, 0-50%B over 60 min, 25 mL/min, 41x350 mm C18 column. Fractions (one/min) 44-46 were combined and concentrated to dryness to afford yellow solids (93 mg, 62%). m.p. 172-175 (dec) °C; ^{1}HNMR (CD_3OD) δ 7.64 (d, J = 8.3 Hz, 2H, ArH), 7.50 (d, J = 7.7 Hz, 1H, ArH), 7.26 (m, 4H, ArH), 7.03 (d, J = 8.2 Hz, 1H, ArH), 6.89 (s, 2H, ArH), 5.45 (m, 1H, CH-4), 4.50 (m, 1H, CH-3), 3.50 (d, J = 5.6 Hz, 2H, NCH_2) 2.30-2.00 (m , 4H, CH_2); IR

(KBr) cm^{-1} 3395, 3347, 1698, 1680, 1637, and 1558. Anal. Calcd. for $C_{29}H_{28}N_2O_9 \circ 1.5H_2O \circ 1.25C_2HF_3O_2$: C, 52.69; H, 4.53; N, 3.90. Found: C, 52.68; H, 4.28; N, 3.90. LRFAB (M + 1) : 549.

(±)-*Trans*-N-(1,1-Dimethylethoxycarbonyl-3-(4-hydroxybenzamido)-4-[4-(6-carboxy-2-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy] pyrrolidine (COMPOUND 644)



Trans-N-t-butoxycarbonyl-3-(4-benzyloxybenzamido)-4-[4-(2-benzyloxy-6-benzyloxycarbonylbenzoyl)-3,5-dibenzyloxy benzoyloxy]pyrrolidine (COMPOUND 643).

4-[4-(2-benzyloxy-6-benzyloxycarbonylbenzoyl)]-3,5-dibenzyloxybenzoic acid (1.47 mmol, 996 mg) and 15 mL anhydrous CH_2Cl_2 in a dry round-bottom flask were cooled in an ice/water bath under N_2. To this was added oxalyl chloride (2.87 mol, 0.25 mL) and 5 dr ps of DMF. This was allowed to stir for 2 hours while the bath melted. TLC (2:1

hexanes:EtOAc) indicated complete formation of the acid chloride. The solvent was removed *in vacuo*.

In a 200 mL dry round-bottom flask was added (±)-*trans*-N-*t*-butoxycarbonyl-3-(4-benzyloxybenzamido)-4-hydroxypyrrolidine (1.26 mmol, 500 mg) in 12 mL anhydrous CH_2Cl_2 under N_2. To this was added triethylamine (3.6 mmol, 0.5 mL) and DMAP (150 mg). A solution of the acid chloride generated above in 10 mL anhydrous CH_2Cl_2 was added *via* cannula. This was allowed to stir under N_2 at room temperature overnight. The reaction mixture was then diluted with CH_2Cl_2, washed with sat. $NaHCO_3$, brine, then dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography using 5% acetone / CH_2Cl_2 as the eluent. Compound 643 (1.08 mmol, 1.15 g) was obtained in 86% yield.

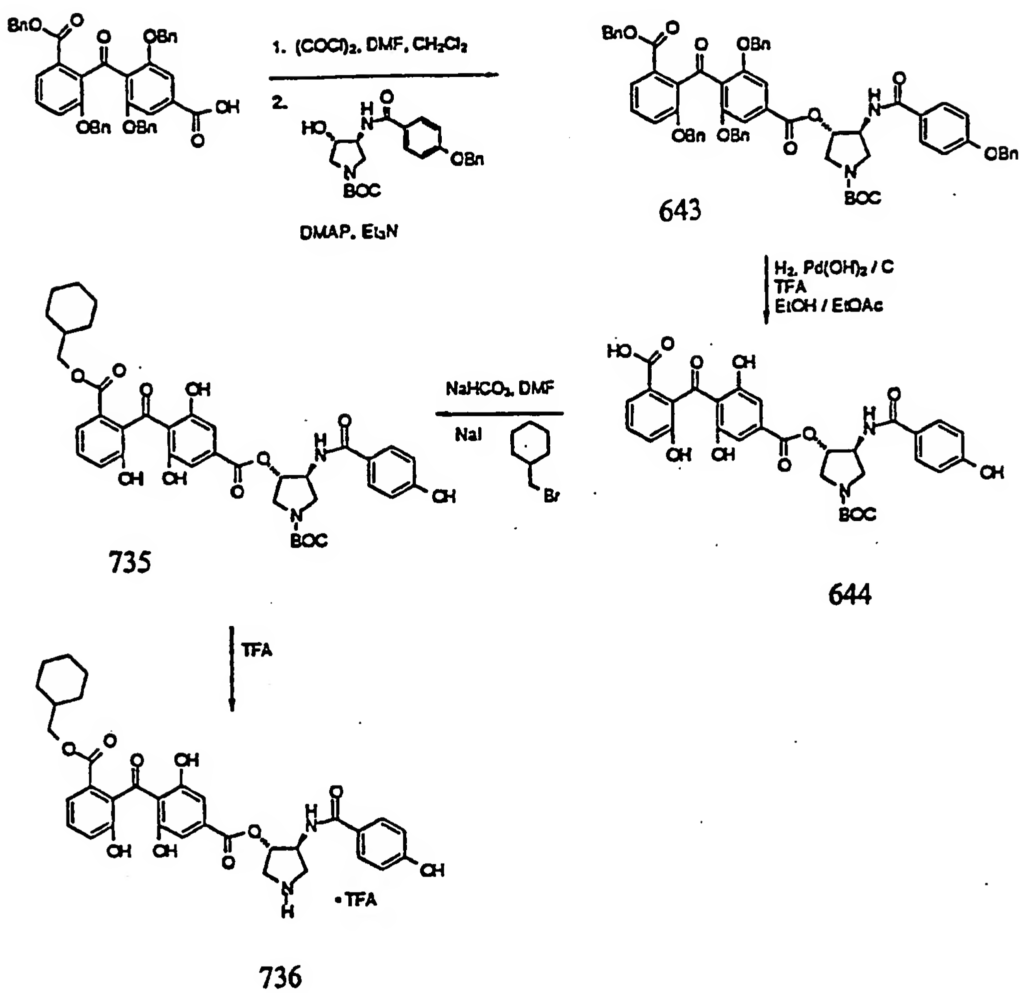
(±)-*Trans*-N-(1,1-Dimethylethoxycarbonyl)-3-(4-hydroxybenzamido)-4-[4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy] pyrrolidine (COMPOUND 644).

To a 500 mL 3-neck round-bottom flask was added (±)-*trans*-N-1,1-dimethylethoxycarbonyl-3-(4-benzyloxybenzamido)-4-[4-(2-benzyloxy-6-benzyloxycarbonylbenzoyl)-3,5-dibenzyloxy benzoyloxy]pyrrolidine (Compound 643, 1.02 mmol, 1.08 g) in 17 mL EtOAc and 70 mL ethanol under N_2. To this was added trifluoroacetic acid (2.55 mmol, 0.20 mL) and $Pd(OH)_2/C$ (730 mg) followed immediately by introduction of H_2 at 1 atmosphere. After a reaction time of 3.5 hours, the reaction was flushed with N_2 and filtered through Celite, rinsing with ethanol. Following concentration *in vacuo*, crude product (Compound 644, 644 mg) was obtained in quantitative yield. A small portion was purified *via* HPLC (21 x 250 mm C18 column, gradient %B = 0 to 50 over 60 min. where A = 0.1% TFA, 5% CH_3CN in water and B = CH_3CN, 15 mL/min. UV = 254 nm) for characterization and the remainder was used crude in subsequent reactions. m.p. 196°C (dec). IR (KBr) 3375(br),

2978, 1704, 1660, 1637, 1607, 1506, 1426, 1368, 1231 cm^{-1}. ^1H NMR CD_3OD, δ 8.52 (d, 1H), 7.72 (d, 2H), 7.49 (d, 1H), 7.26 (t, 1H), 7.01 (d, 1H), 6.91 (s, 2H), 6.80 (d, 2H), 5.40 (m, 1H), 4.63 (m, 1H), 3.87 (m, 2H), 3.50 (m, 2H), 1.47 (s, 9H). HRMS (M + 1) cacld for $C_{31}H_{31}N_2O_{12}$ 623.2, found 623.2 Anal. Calcd for $C_{31}H_{30}N_2O_{12}$ • 1.5 H_2O: C, 57.317; H, 5.120; N, 4.312. Found: C, 57.26: H, 5.18; N, 4.47.

(±)-*Trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-cyclohexylmethoxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine trifluoroacetic acid salt

(COMPOUND 736)



(±)-*Trans*-N-1,1-dimethylethoxycarbonyl-3-(4-benzyloxybenzamido)-4-[4-(2-benzyloxy-6-benzyloxycarbonylbenzoyl)-3,5-dibenzyloxy benzoyloxy]pyrrolidine (COMPOUND 643)

4-[4-(2-benzyloxy-6-benzyloxycarbonylbenzoyl)]-3,5-dibenzyloxybenzoic acid (1.47 mmol, 996 mg) and 15 mL anhydrous CH_2Cl_2 in a dry round-bottom flask were cooled in an ice/water bath under N_2. To this was added oxalyl chloride (2.87 mol, 0.25 mL) and 5 drops of DMF. This was allowed to stir for 2 hours while the bath melted. TLC (2:1 hexanes:EtOAc) indicated complete formation of the acid chloride. The solvent was removed *in vacuo*.

In a 200 mL dry round-bottom flask was added (±)-*trans*-N-1,1-dimethylethoxycarbonyl-3-(4-benzyloxybenzamido)-4-hydroxy pyrrolidine (1.26 mmol, 500 mg) in 12 mL anhydrous CH_2Cl_2 under N_2. To this was added triethylamine (3.6 mmol, 0.5 mL) and DMAP (150 mg). A solution of the acid chloride generated above in 10 mL anhydrous CH_2Cl_2 was added *via* cannula. This was allowed to stir under N_2 at room temperature overnight. The reaction mixture was then diluted with CH_2Cl_2, washed with sat. $NaHCO_3$, brine, then dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography using 5% acetone / CH_2Cl_2 as the eluent. Compound 643 (1.08 mmol, 1.15 g) was obtained in 86% yield.

(±)-*Trans*-N-1,1-dimethylethoxycarbonyl-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-carboxybenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine (COMPOUND 644)

To a 500 mL 3-neck round-bottom flask was added (±)-*trans*-N-1,1-dimethylethoxycarbonyl-3-(4-benzyloxybenzamido)-4-[4-(2-benzyloxy-6-benzyloxycarbonylbenzoyl)-3,5-dibenzyloxy benzoyloxy]pyrrolidine (Compound 643, 1.02 mmol, 1.08 g) in 17 mL EtOAc and 70 mL ethanol under N_2. To this was added trifluoroacetlc acid (2.55 mmol, 0.20 mL) and $Pd(OH)_2$ / C (730 mg) followed immediately by introduction of H_2 at 1

atmosphere. After a reaction time of 3.5 hours, the reaction was flushed with N_2 and filtered through Celite, rinsing with ethanol. Following concentration *in vacuo*, crude product (Compound 644, 644 mg) was obtained in quantitative yield. A small portion was purified *via* HPLC (21 x 250 mm C18 column, gradient %B = 0 to 50 over 60 min. where A = 0.1% TFA, 5% CH_3CN in water and B = CH_3CN, 15 mL/min. UV = 254 nm) for characterization and the remainder was used crude in subsequent reactions. m.p. 196°C (dec). IR (KBr) 3375(br), 2978, 1704, 1660, 1637, 1607, 1506, 1426, 1368, 1231 cm^{-1}. ^1H NMR CD_3OD, δ 8.52 (d, 1H), 7.72 (d, 2H), 7.49 (d, 1H), 7.26 (t, 1H), 7.01 (d, 1H), 6.91 (s, 2H), 6.80 (d, 2H), 5.40 (m, 1H), 4.63 (m, 1H), 3.87 (m, 2H), 3.50 (m, 2H), 1.47 (s, 9H). LRMS (M + 1) cacld for $C_{31}H_{31}N_2O_{12}$ 623.2, found 623.2. Anal. Calcd for $C_{31}H_{30}N_2O_{12}$ • 1.5 H_2O: C, 57.317; H, 5.120; N, 4.312. Found: C, 57.26; H, 5.18; N, 4.47.

(±)-*Trans*-N-t-butoxycarbonyl-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-cyclohexylmethoxycarbonylbenzoyl)-3,5-dihydroxy-benzoyloxy]pyrrolidine (COMPOUND 735)

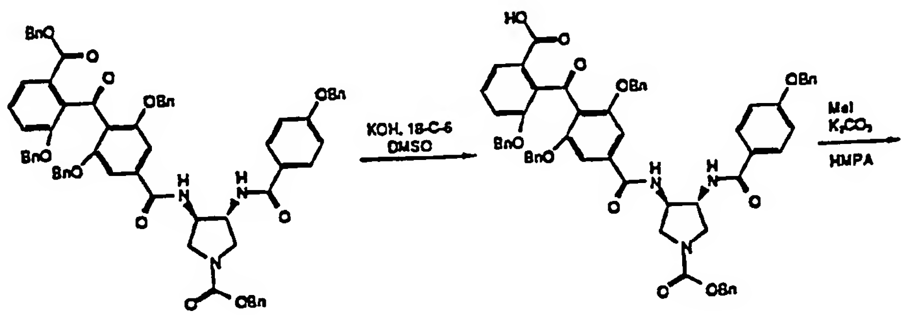
To a round-bottom flask was added (±)-*trans*-N-1,1-dimethylethoxycarbonyl-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-carboxybenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine (Compound 644, 0.18 mmol, 111.6 mg) in 5 mL DMF. To this was added $NaHCO_3$ (0.26 mmol, 22 mg), NaI (0.31 mmol, 47 mg) and cyclohexylmethyl bromide (0.90 mmol, 0.13 mL). This was allowed to stir under N_2 for 7 days. During this time additional cyclohexylmethyl bromide (total of 25 additional equivalents, 0.67 mL) was added as well as one addition of NaI (2 eq., 55 mg). The reaction was heated to 45°C for 24 hours then at 55° for 32 hours. The reaction mixture was diluted with EtOAc and washed with brine 3 times. The aqueous layer was back extracted with EtOAc and the organic layers combined and dried over $MgSO_4$ then concentrated *in vacuo*. The crude product was purified *via* flash column chromatography using a gradient eluent system 5 - 50% MeOH in CH_2Cl_2 to isloate (±)-*trans*-N-1,1-dimethylethoxycarhonyl-3-

(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-cyclohexylmethoxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine (Compound 735, 52 mg, 40% yield).

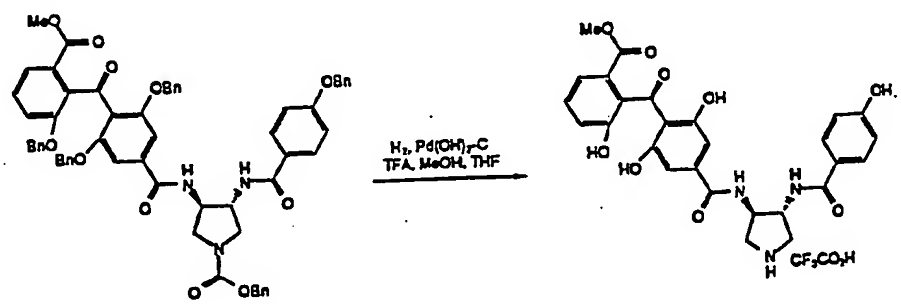
(±)-*Trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-cyclohexylmethoxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine trifluoroacetic acid salt (COMPOUND 736)

(±)-*Trans*-N-1,1-dimethylethoxycarbonyl-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-cyclohexylmethoxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine (Compound 735, 52 mg, 0.072 mmol) was dissolved in 0.80 mL neat trifluoroacetic acid and allowed to stir at room temperature under N_2 for 45 minutes at which time TLC (75% CH_2Cl_2, 24% MeOH, 1% (10% aq) NH_4OH) indicated the reaction was complete. This was diluted with toluene and concentrated *in vacuo* to yield crude product (55 mg, 97% yield). Purification *via* HPLC (21 x 250 mm C18 column, gradient %B = 0 to 100 over 60 min. where A = 0.1% TFA, 5% CH_3CN in water and B = CH_3CN, 15 mL/min. UV = 254 nm) yielded (±)-*trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-(cyclohexylmethoxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy] pyrrolidine trifluoroacetic acid salt (Compound 736, 33 mg, 58% yield) as a yellow solid. m.p. 154-160°C (dec.). IR (KBr) 3247 (br), 2931, 2854, 1679, 1636, 1607, 1543, 1508, 1426, 1371, 1303, 1202 cm^{-1}. ^1H NMR, CD_3OD, δ, 7.75 (d, 2H), 7.48 (d, 1H), 7.29 (t, 1H), 7.02 (d, 1H), 6.99 (s, 2H), 6.83 (d, 2H), 5.63 (m, 1H), 4.76 (m, 1H), 3.98 (dd, 1H), 3.91 (d, 2H), 3.84 (dd, 1H), 3.59 (m, 2H), 1.61 (m, 5H), 1.45 (m, 1H), 1.13 (m, 3H), 0.89 (m, 2H). LRMS (M + 1) calcd for $C_{33}H_{35}N_2O_{10}$ 619.23, found 618.9 Anal. Calcd for $C_{33}H_{34}N_2O_{10} \cdot 1.3C_2HF_3O_2 \cdot H_2O$: C, 54,48; H, 4.79; N, 3.57. Found: C, 54.68; H, 4.67; N, 3.71.

(±)-*Trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-meth xycarbonylbenzoyl)-3,5-dihydroxybenzamido]pyrrolidin trifluoroacetic acid salt (COMPOUND 739)



640 737



738 739

COMPOUND 737

A mixture of Compound 640 (110 mg, 0.1 mmol, see Compound 563 for preparation), KOH (28 mg, 0.5 mmol), and 18-C-6 (13 mg, 0.05 mmol) in DMSO (1 mL) was stirred at 50°C for 3 h, cooled to room temperature, and EtOAc (10 mL), followed by 1N HCl (1 mL), was added. The mixture was washed with H_2O (3 x 10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. The residue was purified by preparative TLC (SiO_2, 10% MeOH in CH_2CI_2) to give a white solid (100 mg, 98%).

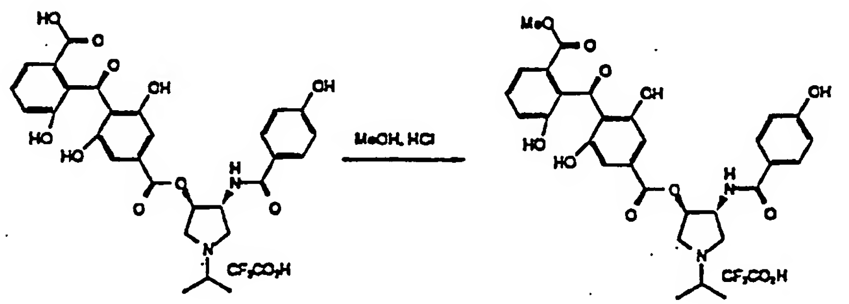
COMPOUND 738

A mixture of Compound 737 (150 mg, 0.15 mmol), K_2CO_3 (41 mg. 0.3 mmol), and MeI (0.093 mL) in HMPA (0.75 mmol) was stirred at 40°C for 3 h, cooled to room temperature, and diluted with EtOAc (10 mL). The mixture was washed with H_2O (3 x 10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. The residue was purified by preparative TLC (SiO_2, MeOH: CH_2CI_2 = 1:20) to give a white solid (137 mg, 89%).

COMPOUND 739

$Pd(OH)_2$ on carbon (COMPOUND 739) (20 wt%, contains ≤50% moist, 18 mg, 0.013 mmol), trifluoroacetic acid (15mg 0.13 mmol), and MeOH (1.3 mL) was added to a solution of Compound 738 (135 mg, 0.13 mmol) in THF (1.3 mL) and the mixture was stirred under 1 atm H_2 contained in a balloon at room temperature for 24 h. The mixture was filtered through Celite and the filtrate was evaporated. The residue was purified by HPLC on a C18 column to give an yellow solid (69 mg, 77%). IR (KBr, cm-1): 1674, 1636, 1607. FABMS: M/Z 536 (M + 1).

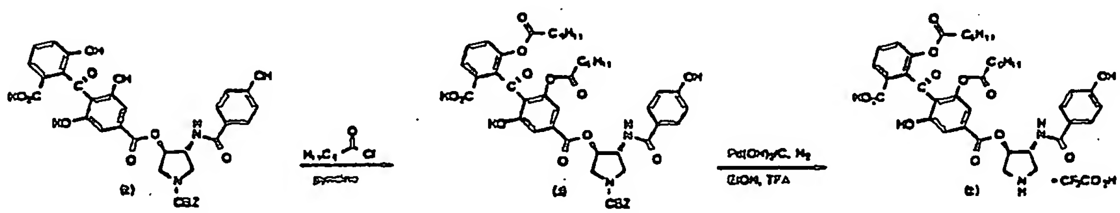
(±)-1-1-methylethyl-*trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-methoxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidine trifluoroacetic acid salt (COMPOUND 740)



592 740

HCl in dioxane (4 M, 0.165 mL, 0.66 mmol) was added to a solution of Compound 592 (90 mg, 0.13 mmol) in anh. MeOH (4 mL) and the mixture was stirred at 50°C for 20 h. The resultant mixture was evaporated and the residue was purified by HPLC on a C18 column to give recovered Compound 592 (21 mg, 23%) and Compound 740 (49 mg, 54%) as a yellow solid. IR (KBr, cm-1): 1674, 1636, 1607. FABMS: 579 (M + 1).

(±)-*Trans*-3-(4-hydroxybenzamido)-4-[4-(2-hexanoyloxy-6-hydr xycarb nylbenzoyl)-3-hydroxy-5-hexanoyloxybenzoyloxy] pyrrolidinium trifluoroacetate (COMPOUND 742)



741 742

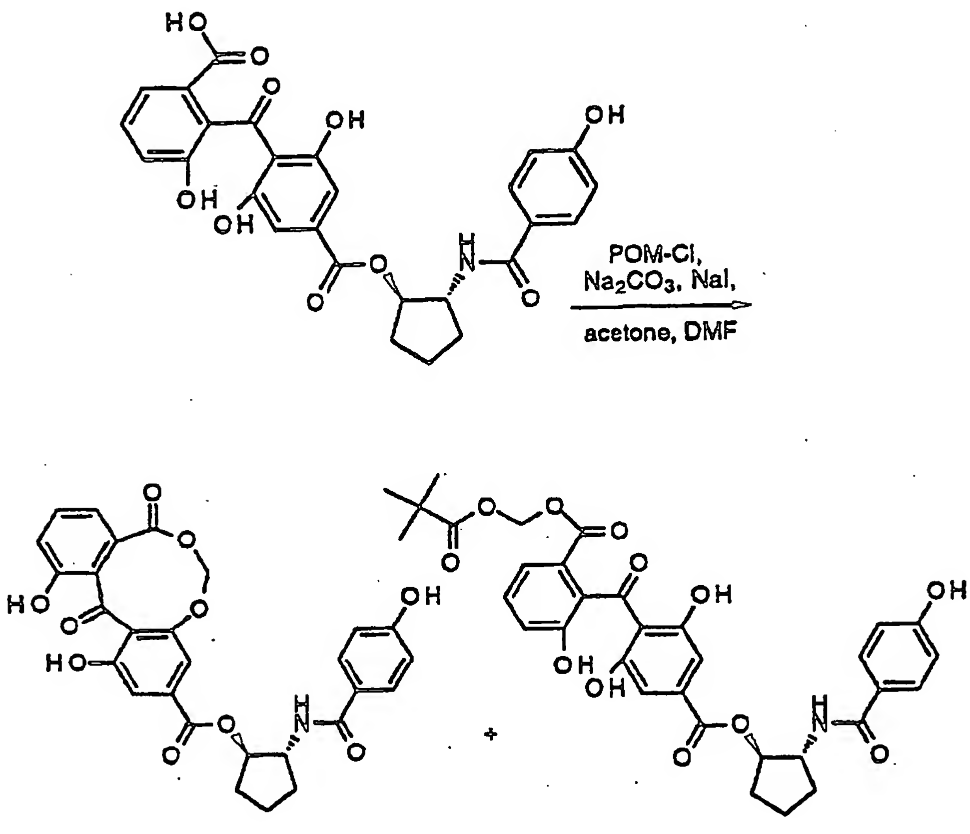
(±)-*Trans*-3-(4-hydroxybenzamido)-4-[4-(2-hexanoyloxy-6-hydroxycarbonylbenzoyl)-3-hydroxy-5-hexanoyloxybenzoyloxy]-N-benzyloxycarbonylpyrrolidine (COMPOUND 741)

Hexanoyl chloride (64 µL, 0.457mmol) was added to a stirred solution of (±)-*trans*-3-(4-hydroxybenzamido)-4[4(2-hydroxy-6-hydroxycarbonylbenzoyl)-3,5-dihydroxybenzoyloxy]-N-benzyloxycarbonylpyrrolidine (0.050 g, 0.076 mmol) in anhydrous pyridine (2 mL) at 0°C under N_2. The resulting solution was then allowed to warm to room temperature and stir for 16 h. MeOH (3 mL) was added and the solution concentrated *in vacuo*. The residue (0.068 g) was used without further purification.

(±)-*Trans*-3-(4-hydroxybenzamido)-4-[4-(2-hexanoyloxy-6-hydroxycarbonylbenzoyl)-3-hydroxy-5-hexanoyloxybenzoyloxy] pyrrolidinium trifluoroacetate (COMPOUND 742)

Moist palladium hydroxide on carbon (68 mg, 20 % Pd) was added to a stirred solution of (±)-*trans*-3-(4-hydroxybenzamido)-4-[4-(2-hexanoyloxy-6-hydroxycarbonyl benzoyl)-3-hydroxy-5-hexanoyloxybenzoyloxy]-N-benzyloxy carbonylpyrrolidine (0.068 g) in EtOH (2 mL) and TFA (0.25 mL). The mixture was stirred under 1 atm. of hydrogen for 16 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was chromatographed on a 41x300 mm C18 column (solvent A: 95:5 water/acetonitrile + 0.1% TFA; solvent B: 100% acetonitrile; gradient: 0 - 100% B over 60 m; flow: 25 mL/m) affording the title compound (5.2 mg, 8%) as a yellow oil. FABMS Calcd. for $C_{38}H_{42}N_2O_{12}$ (m/z, M^+ + 1): 718.2738; found 718.2808.

Anti-1-[4-(2-[1,1-Dimethylethylcarboxy-m thyl xycarbonly]-6-hydroxybenzoly)-3,5-dihydroxybenzoyloxy]-2-(4-hydroxybenzamido)cyclopentane (COMPOUND 759)

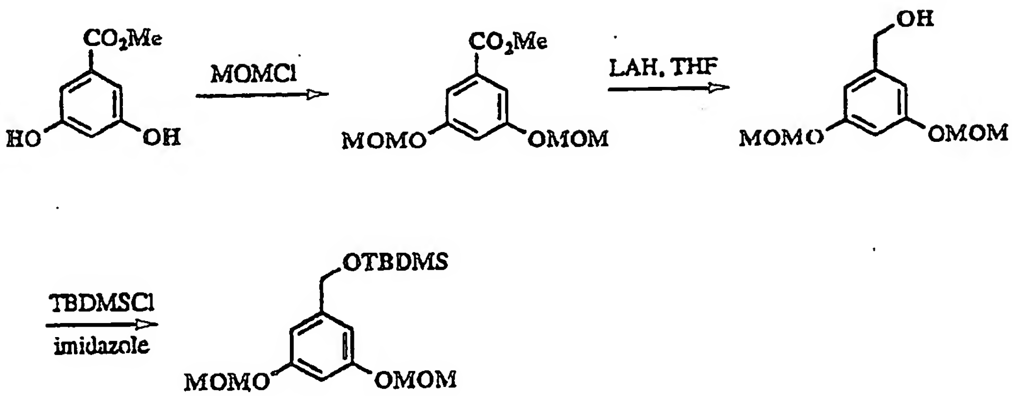


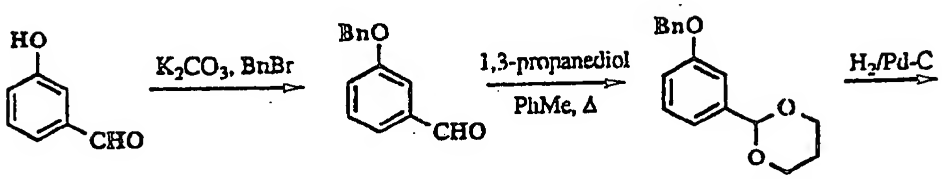
759

To a stirred solution of starting acid (0.19 mmol, 100 mg) in acetone (2 mL)/N,N-dimethylformamide (DMF, 2 mL) were added sodium iodide (NaI, 0.48 mmol, 72 mg), sodium carbonate (Na_2CO_3), 0.29 mmol, 30 mg), and chloromethyl pivalate (POM-Cl, 1.92 mmol, 290 mg). The reaction flask was purged with nitrogen gas and stirred at room temperature for 7 hours. The reaction, monitored by TLC showed no remaining starting material after 7 hours. The deep yellow reaction

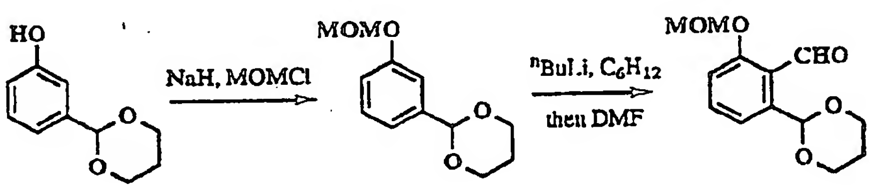
mixture was diluted with ethyl acetate (150 mL), transferred to a separatory funnel, washed with water (50 mL) and brine (50 mL0, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Compound 759 was isolated (8 mg, 6.6% yield) from the crude reaction mixture by flash column chromatography. The crude reaction mixture also contained the tricyclic material shown in the reaction scheme. The product was further purified by preparative plate purification yielding the product as a light yellow solid.

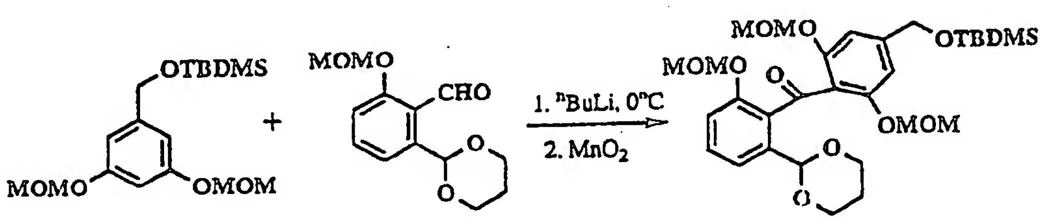
MOM-Protected Benzophen ne

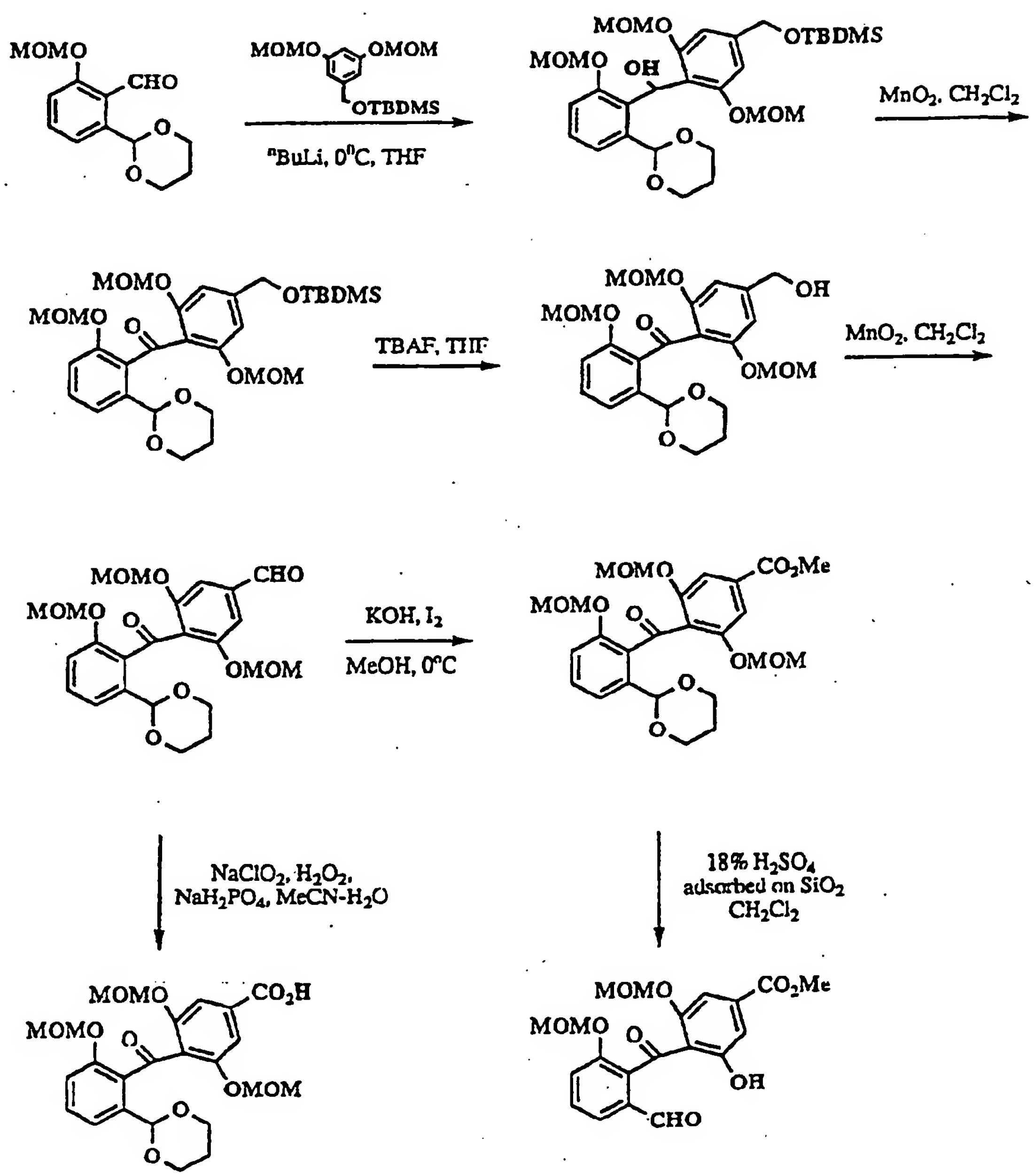


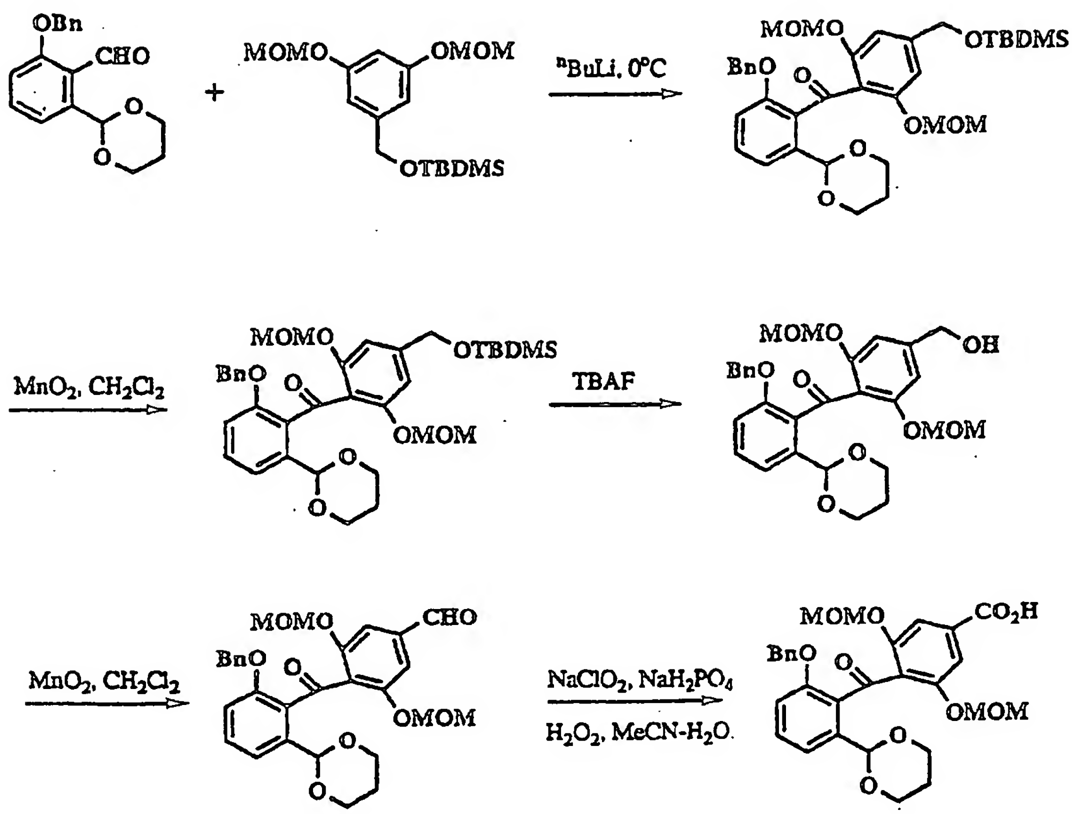


SPC 104090

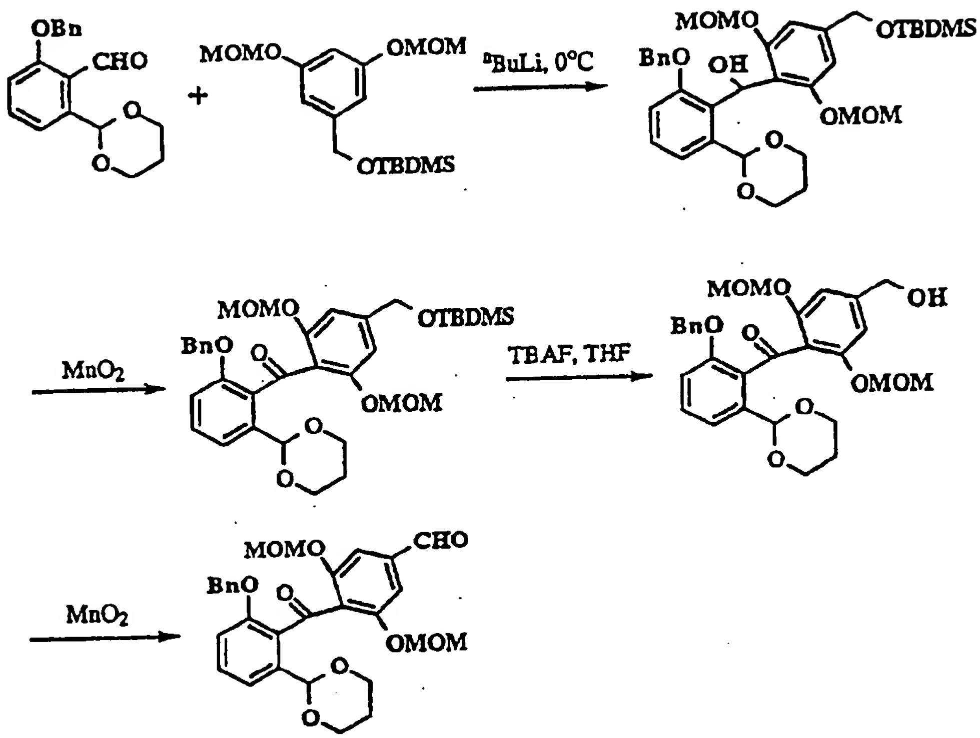





MOMO
CHO
O
O
MOMO
OMOM
OTBDMS
^nBuLi, 0°C, THF
MOMO
MOMO
OH
OTBDMS
OMOM
MnO_2, CH_2Cl_2
TBAF, THF
OH
CHO
KOH, I_2
MeOH, 0°C
CO_2Me
$NaClO_2$, H_2O_2,
NaH_2PO_4, $MeCN$-H_2O
18% H_2SO_4
adsorbed on SiO_2
CH_2Cl_2
CO_2H


OBn
CHO
MOMO
OMOM
OTBDMS
ⁿBuLi, 0°C
BnO
MnO2, CH2Cl2
TBAF
OH
CHO
NaClO2, NaH2PO4
H2O2, MeCN-H2O
CO2H

[4-(2-Benzyloxy)-6-(1,6-dioxanyl)benzoyl]-3,5-dimethoxy methoxybenzaldehyde



N-BuLi (18.5 ml of a 2.5 M solution in hexanes, 40.2 mmol) was added dropwise to a solution of MOM diether (15.8g, 46.3mmol) in dry THF at 0°C over a 5 min period. Stirring was then continued for 60 min whereupon this solution was added *via* cannula to a solution of aldehyde (12.0g, 40.2 mmol) in anhydrous THF at 0°C. The light yellow solution was allowed to stir at 0°C for 2hr and then allowed to warm to ambient temperature and stirring continued overnight. The reaction mixture was quenched with saturate ammonium chloride solution and diluted with ethyl acetate. The layers were separated and the aqueous layer extracted with ethyl acetate. The combined organics were washed with brine dried ($MgSO_4$) and evaporated. The residue was chromatographed (2:1 hexanes-ethyl acetate) to afford the alcohol as a foam (18.8g, 73%).

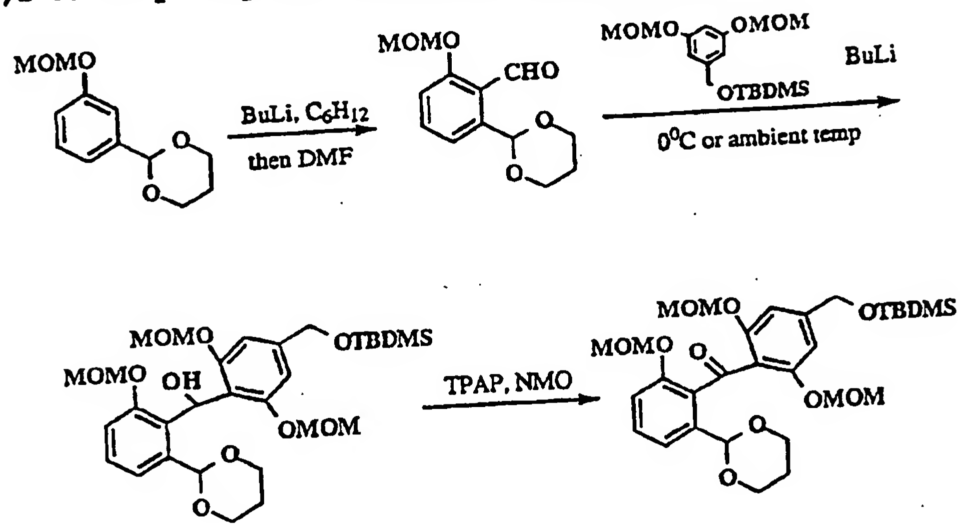
The alcohol above (18.7g, 29.2mmol) was dissolved in methylene chloride and MnO_2 (25.4g, 0.292mol) added in

portions. The reaction mixture was allowed to stir overnight at ambient temperature at which time an additional 10g of MnO_2 was added and stirring continued for 2 days. The catalyst was removed by filtration through Celite and washed with more methylene chloride. The filtrates were evaporated to give the benzophenone (17.4g, 93%) as a white foam.

TBAF (34.7ml of a 1M solution in THF, 34.8mmol) was added to a stirred solution of the above prepared benzophenone (18.5 g, 29.0mmol) in anhydrous THF. After 1.5hr, brine was added and extracted twice with ethyl acetate. The aqueous layer was further extracted with methylene chloride and the ethyl acetate mixture backwashed with brine. The organics were all combined, dried ($MgSO_4$) and evaporated. The residue was chromatographed (SiO_2, 2:1 ethyl acetate-hexanes) to afford the alcohol (13.4g, 8*%) as a white solid: mp 130-2°C; anal. calcd. for $C_{29}H_{32}O_9 . 0.2H_2O$ C 65.95, H 6.18. Found C 65.73, H 6.12.

MnO_2 (ca. 10g) was added in portions to a stirred solution of the above alcohol (13.1g) in methylene chloride and allowed to stir for 2 days at ambient temperature. The catalyst was removed by filtration through Celite and the filtrates were evaporated to yield the aldehyde (12.7g, 97%) as a white solid. The crude H NMR looked clean. An analytical sample could be prepared by crystallization from ethyl acetate: mp 134-6°C; anal. calcd. for $C_{29}H_{30}O_9 . 0.1H_2O$ C 66.43, H 5.81. Found C 66.23, H 6.18.

2'-(1,6-Dioxanyl)-6'-methoxymethoxy-2,6-di(methoxymethoxy)-4-(1,1-dimethylethylsilyloxymethyl)benzophenon



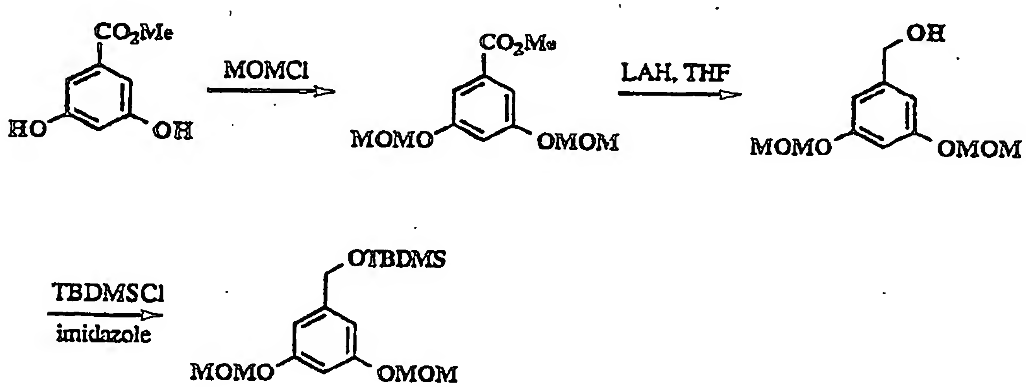
N-BuLi (10.9ml of a 1.6M solution in hexanes, 17.5mmol) was added dropwise to a stirred solution of acetal (3.65g, 15.9mmol) in anhydrous cyclohexane at ambient temperature. The mixture (which gummed up) was stirred for 15 min. whereupon dry DMF (3.69ml, 47.6mmol) was added dropwise and stirred for an additional 15 min., Quenched upon addition of brine and diluted with ethyl acetate. The organics were separated and washed with brine and deionized water, dried ($MgSO_4$) and evaporated to a light yellow gum. The aldehyde (4.0 g, 100%) was used without further purification.

N-BuLi (6.80mol of a 1.6M solution in hexanes, 10.9mmol) was added dropwise to a solution of MOM diether (3.4g, 9.93mmol) in dry THF at 0°C over a 5 min period. Stirring was then continued for 15 min whereupon this solution was added *via* cannula to a solution of the above prepared aldehyde (2.63g, 10.4mmol) in anhydrous THF at 0°C. The light yellow solution was then allowed to warm to ambient temperature and stirred overnight. This was quenched with brine and diluted with ethyl acetate. The layers were separated and the aqueous layer extracted with ethyl acetate. The combined organics were washed with brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed (2:1 hexanes-ethyl acetate) to

afford the major product alcohol as a gum (2.5g, 41%). Some impure aldehyde (500mg) was also recoved.

N-Methyl morpholine oxide (0.80g, 6.81mmol) was added to a mixture of the above prepared alcohol (2.7g, 4.54mol) and crushed 4A molecular sieves (which had been placed in a 110°C oven for several hours) in dry methylene chloride. After 30 min TPAP (160mg, 0.454mmol) was added and the resulting solution stirred at ambient temperature for 2 days. Silica was added and the solvent removed *in vacuo* and placed on a dry packed column of silica and eluted with 3:1 hexane-ethyl acetate. The benzophenone (2.34g, 87%) was isolated as a clear colorless oil: anal. calcd. for $C_{30}H_{44}O_{10}Si.0.3H_2O$ C 60.24, H 7.51. Found C 59.89, H 7.56.

3,5-Di(methoxymethyleneoxy)-1,1-dimethylethlsilyl oxymethylbenzene



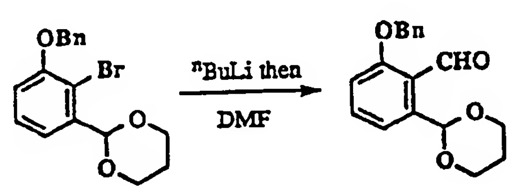
MOMCl (29.8mol, 0.393mol) was added dropwise to a 0°C solution of methyl 3,5-dihydroxybenzoate (30g, 0.178mol) and Hunigs base (57.6g, 77.7mol, 0.446mol) in methylene chloride. After the final addition the reaction mixture was allowed to warm to ambient temperature and stirred overnight. This was poured into deionized water, the organics separated and washed with 10% aqueous copper sulphate solution. The organic layer was dried ($MgSO_4$), evaporated and chromatographed (SiO_2, 15:1 to 9:1 hexane-ethyl acetate, gradient elution). The major product was isolated as a clear colorless oil (34.5g, 75%) and

used as is in the next step.

The ester (36.0g, 0.14mol) was dissolved in anhydrous THF and added dropwise to a stirred solution of lithium aluminum hydride (183ml of a 1.0M solution in THF) in dry THF> After the final addition, stirring was continued for 2hr whereupon deionized water (8ml), 15% aqueous NaOH (8ml) and deionized water (28ml) were sequentially added dropwise. The resulting suspension was stirred for 2hr and filtered. The solids were washed with ethyl acetate and the filtrates evaporated to provide the alcohol as a clear colorless oil (34g) which was used in the next step without further purification.

A solution of TBDMSCl (23.3g, 0.154mol) in methylene chloride was added to a stirred mixture of imidazole (10.5g, 0.154mol) and the above prepared alcohol (32.06g, 0.140mol) in methylene chloride. The reaction mixture was allowed to stir at ambient temperature overnight and poured into DI water. The organics were separated washed with 10% aqueous copper sulphate solution, brine and dried ($MgSO_4$) and evaporated. The residue was chromatographed (SiO_2, 10:1 hexane-ethyl acetate) to provide the title compound as a clear colorless oil (38.9g, 81%): anal. calcd. for $C_{17}H_{30}Si)_5$ C 59.62, H 8.83. Found C 59.63, H 8.75.

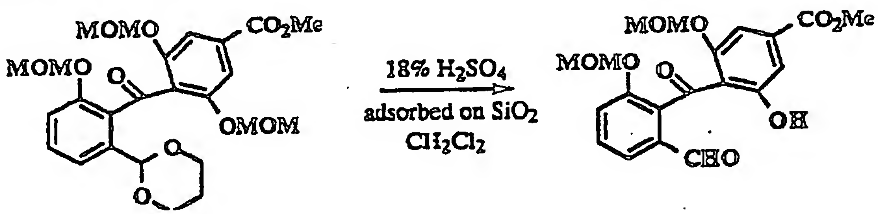
2-[2-Formyl-3(benzyloxy)phenyl]-1,3-dioxane



N-BuLi (3.98ml of a 1.6M solution in hexanes, 6.36mmol) was added dropwise over 10-15 min to a solution of arylbromide (2.02g, 5.78mmol) in dry THF at -78°C. After the final addition the mixture was stirred for an additional 30 min whereupon ahydrous DMF (4.48ml, 57.8mmol; 10 equivalent) was added dropwise over a period of 10min. The resulting solution

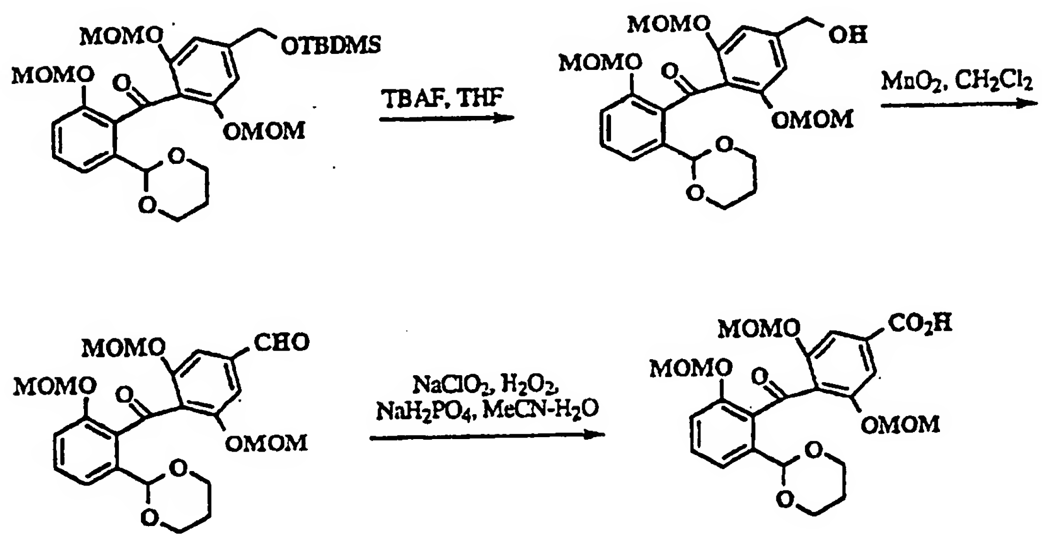
was stirred -78°C for 4hr and allowed to slowly warm to ambient temperature and allowed to stir overnight (16hr). The reaction was quenched upon addition of saturated ammonium chloride soution and diluted with ethyl acetate. The aqueous was separated and extracted with ethyl acetate. The combined organics were sequentially washed with brine and water several times, dried ($MgSO_4$) and evaporated to afford a gum which was chromatographed (SiO_2, 1:1 to 2:1 methylene chloride-hexanes, gradient elution) and the major component (title compound) isolated as an oil, which crystallised upon standing: mp 85-7°C; anal. calcd. for $C_{18}H_{18}O_6$ C 72.47, H 6.08. Found C 72.26, H. 5.86.

Methyl 4-[6-Formyl-2-methoxymethoxy-benzoyl]-5-hydroxy-3-methoxymethoxy-benzoate



A solution of ester (1.65g, 3.26mmol) in methylene chloride was added to a stirred mixture of 18% sulphuric acid adsorbed on silica (*ca.* 12g). The reaction mixture was stirred at ambient temperature for 10 hr whereupon solid sodium carbonate was added, stirred for 5 minutes and filtered through a sintered funnel. The solid material was washed with methylene chloride and the filtrates were evaporated. The residue was crystallied from diethyl ether to afford aldehyde ester (1.12g, 63%) as a light yelow solid: mp 106-8°C; anal. calcd. for $C_{20}H_{20}O_9$ C 59.41, H 4.98. Found C 59.71, H. 5.06.

3,5-Di(m thoxymethoxy)-4-(2-methoxymethoxy)-6-(1,6-dioxanyl)benzoic acid



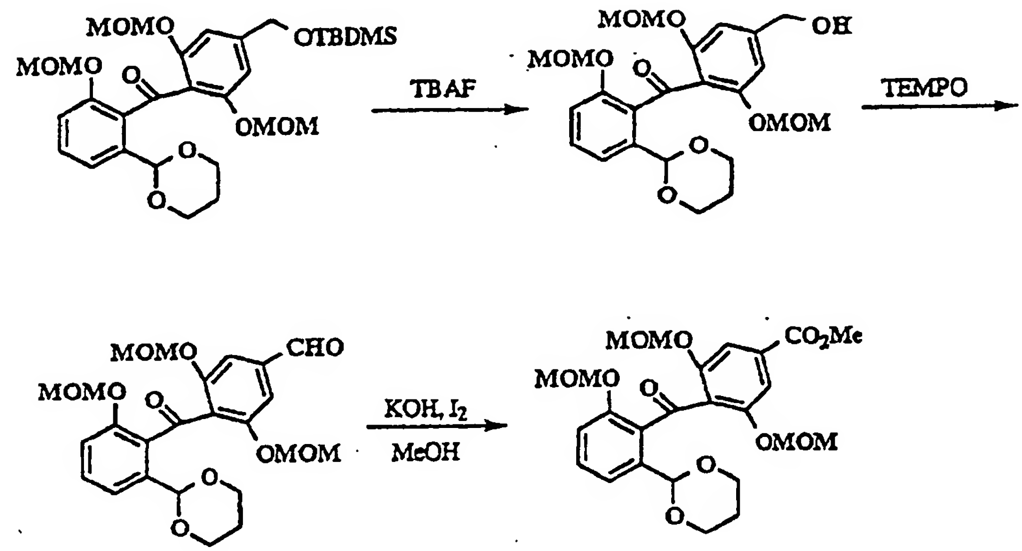
Tetrabutylammonium fluoride (45.0ml of a 1.0M solution in THF, 44.9mmol) was added dropwise to a stirred solution of silylether (22.2g, 37.4mmol) in anhydrous THF (150mol). After stirring for 1hr the reaction was quenched with brine and diluted with ethyl acetate. The organics were separted and the aqueous layer extracted with ethyl acetate. The combined aqueous layers were also extracted with methylene chloride. The combined ethyl acetate extracts were backwashed with brine and added to the methylene chloride layer. These combined organics were dried ($MgSO_4$) and evaporated and the residue chromatographed (SiO,2:1 ethyl acetate-hexanes) to provide the alcohol as an oil (13.0g, 72%) which crystallised upon standing and was used in the next step without further purification.

Manganese dioxide (12g) was added in protions to a stirred solution of the alcohol (14.1g, 29.5mmol) in methylene chloride. The mixture was stirred at ambient temperature for

2 days and the catalyst removed by filtration through celite. The catalyst was washed with futher methylene chloride and the filtrates evaporated to afford teh aldehyde as a white foam (12.2g, 84%).

A solution of the above prepared aldehyde (12.2g, 24.8mmol) and NaH_2PO_4 (1.04g, 8.67mmol; 0.35equiv.) in acetonitrile and deionized water (160ml total volume; 6:1 v/v) was cooled in an ice-bath. Hydrogen peroxide (3ml of a 30% solution on water) was added followed by solid sodium chlorite (4.4g of 80%). This mixture was stirred for 1hr and the solvent was removed *in vacuo*. Deionized water was added and the precipitated solid collected by filtration. This was dried *in vacuo* to give the acid (9.11g). The filtrates were extracted with methylene chloride, dried ($MgSO_4$), evoporated and crystallized from ethyl acetate-hexanes to provide acid (0.8g). These solid materials were combined to give a total yield of 9.91g (79%) of target acid: mp 152-3°C; anal. calcd. for $C_{24}H_{28}O_{11}$ C 58.53, H 5.73. Found C 58.30, H 5.73.

Methyl [3,5-Dimethoxymethoxy-4-(2-methoxymethoxy)-6-(1,6-dioxanyl)benzoylbenzoate



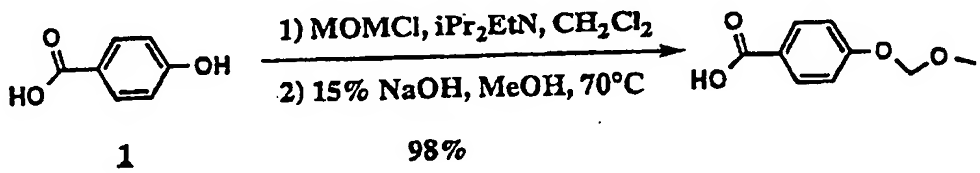
TBAF (7.96ml of a 1.0M solution in THF, 7.96mmol) was added dropwise to a stirred solution of silylether (2.36g, 3.98mmol) in anhydrous THF at ambient temperature. After 1 hr, brine was added and diluted with ethyl acetate. The organics were separated and the aqueous layer extracted with more ethyl acetate. The combined organics were washed with brine, dried ($MgSO_4$) and evoporated to a gum (1.43g, 75%). This material was used in the next step without further purification.

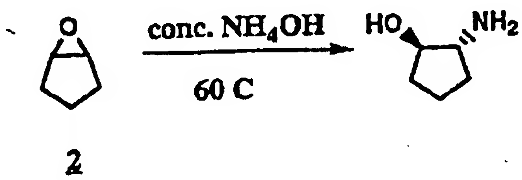
TEMPO (2.3mg, 0.0148mmol) was added to a solution of sodium bromide (46mg, 0.445mmol) and the above prepared alcohol (1.42g, 2.97mmol) in methylene chloride. The reaction mixture was placed in an ice bath and a freshly prepared solution of sodium bicarbonate (37mg, 0.445mmol) in Chlorox (4ml) was added dropwise. Stirring was continued for an additional 30 min whereupon the reaction was quenched with solid sodium sulfite. Deionized water was added to dissolve any suspend solids and the organic layer separated, dried ($MgSo_4$) and evoporated to afford the aldehyde (1.5g) as a gum. This material was used in the next step without further purification.

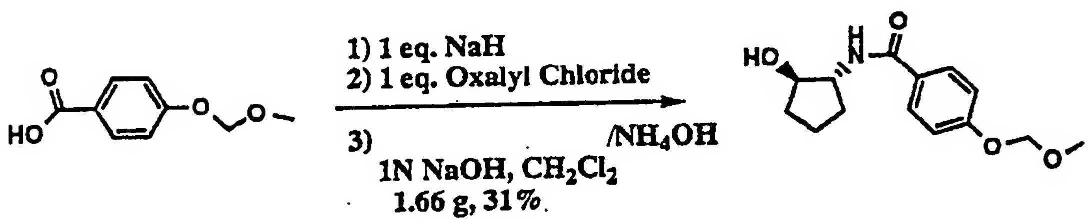
A 0°C solution of potassium hydroxide (0.41g,

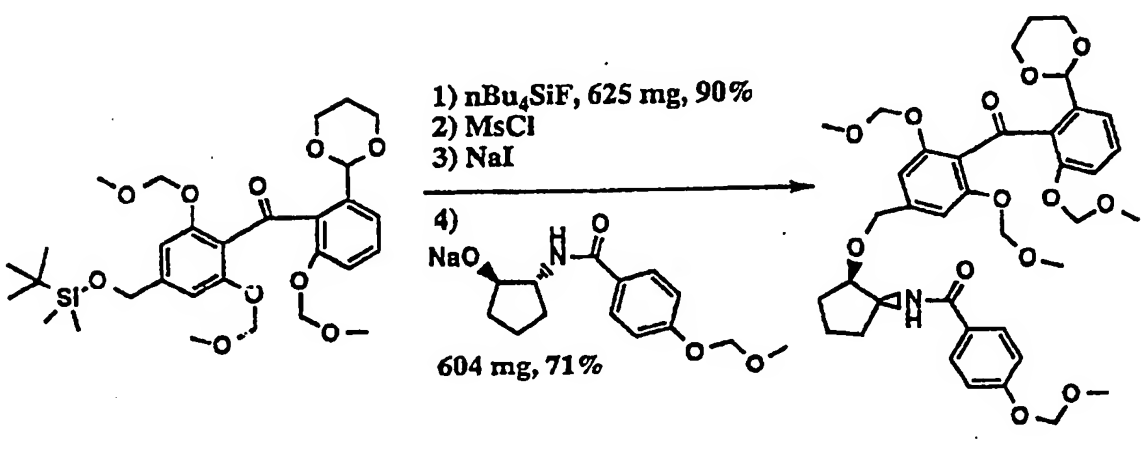
7.23mmol) in methanol was added dropwise to a solution (0°C) of the above prepared aldehyde (1.37g, 2.78mmol) in methanol. This was followed by the dropwise addition of a solution of iodine (0.92g, 3.62mmol) in methanol precooled to 0°C. After the final addition, the reaction mixture was warmed to ambient temperature and allowed to stir for 1hr. The mixture was then neutralised with 1N potassium hydrogen sulfate and the solvents removed *in vacuo*. The residue was partitioned between ethyl acetate and brine. The organics were separted and washed with aqueous sodium thiosulfate, dried ($MgSO_4$) and evaporated. The residue was chromatographed (SiO_2, 8:5 hexane-ethyl acetate) and the ester was isolated (819mg) as a white foam. Alternatively this material could be concentrated and allowed to crystallise upon standing. Mp 104-5°C; anal. calcd. for $C_{25}H_{30}N_{11}$ C 59.28, H 5.97. Found C 59.38, H 6.05.

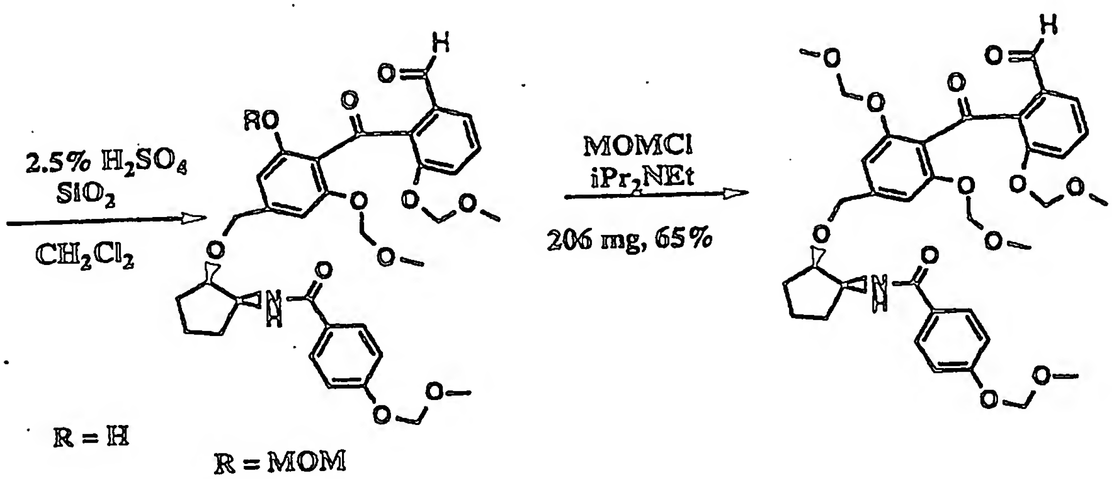
Preparation of *Anti*-1-[4-hydroxycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxyb nzyloxy-2-(4-hydroxybenzamido)cyclop ntan (COMPOUND 728)

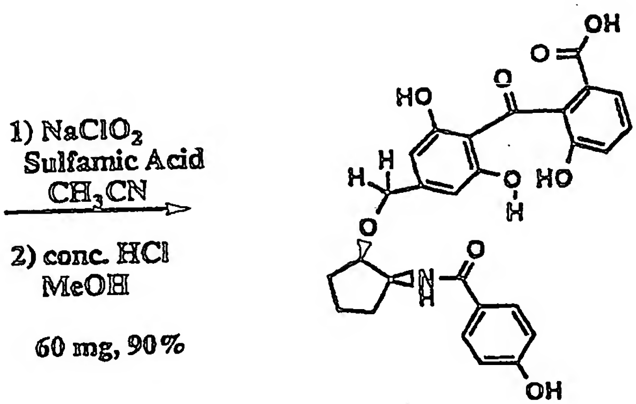









2.5% H2SO4
SiO2
CH2Cl2
MOMCl
iPr2NEt
206 mg, 65%
R = H
R = MOM


1) NaClO2
Sulfamic Acid
CH3CN
2) conc. HCl
MeOH
60 mg, 90%

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4-M thoxymethyleneoxybenzoic acid

To a solution of the 4-hydroxybenzoic acid (10.0 g, 0.072. mol) in CH_2Cl_2 (20 mL) under an atmosphere of nitrogen at 0°C was added N, N-diisopropylethylamine (69.11 ml, 0.394 mol) followed by the dropwise addition of chloromethyl methyl ether (30 mL, 0.394 mol) over 1 hours. The reaction mixture was allowed to stir at room temperature for 48 hours. The reaction mixture was quenched with saturated NH_4Cl (100 ml) and extracted with CH_2Cl_2 (2 X 100 mL). The combined CH_2Cl_2 layers were dried over $MgSO_4$, filtered and the volatiles removed under reduced pressure to provide crude methoxymethyleneoxy 4-methoxymethyleneoxybenzoate.

To a solution of the crude methoxymethyleneoxy 4-methoxymethyleneoxybenzoate in methanol (100 mL) was added 15% NaOH (80 mL) and the mixture was heated at 70°C for 3 hours. The reaction mixture was cooled to 0°C, and the pH was adjusted to 5 with 6N HCl. Filtration of the reaction mixture provided a white solid of the title compound (11.1 g). Extraction of the aqueous phase with ethyl acetate provided an additional 1.1 g of the title compound (12.9 g, 98%).

1-Hydroxy-2-(4-benzyloxybenzamido)cyclopentane

To a suspension of NaH (876 mg, 21.9 mmol, 60% by wt in mineral oil) in anhydrous THF (45 mL) under an atmosphere of nitrogen at 0°C was added a solution of the 4-Methoxymethylene oxybenzoic acid (3.63 g, 19.9 mmol) in anhydrous THF dropwise over 20 minutes. The ice bath was removed and the reaction mixture was allowed to stir for 0.5 hours at room temperature. The reaction mixture was recooled to 0°C and oxalyl chloride (11.0 mL, 21.9 mmol, 2 M in CH_2Cl_2) was added dropwise over 15 minutes. The reaction mixture was allowed to stir for 24 hours. The volatiles were removed under reduced pressure.

A suspension of cyclopentene oxide (1.89 mL, 21.5 mmol) in conc. NH_4OH (9 mL) was heated at 65°C for 3 hours. The reaction mixture was cooled to room temperature and 1 N NaOH (30 mL, 30 mmol) was added. The reaction mixture was allowed to stir at room temperature while nitrogen was bubbled

into the solution (in order to remove ammonia) for 0.5 hours. The reaction mixture was cooled to 0°C and a solution of the above generated acid chloride in dichloromethane (40 mL) was added. The reaction mixture was allowed to stir overnight at room temperature, and then recooled to 0°C and neutralized with 1N HcL. Ethyl acetate (300 mL) was added and the layers were separated. The ethyl acetate layer was washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and the volatiles were removed under reduced pressure. The crude residue was purified using flash column chromatography (silica gel, 2% methanol / chloroform) to provide the title compound as white solid (1.66 g, 31%), mp 91-92°C.

To a solution of the silyl ether (858 mg, 1.45 mmol) in anhydrous THF (10 mL) under an atmosphere of nitrogen was added tetrabutylammonium fluoride (2.89 mL, 2.89 mmol, 1 M in THF) dropwise over 5 minutes. The reaction mixture was allowed to stir for 2 hours at room temperature, and then was diluted with ethyl acetate (150 mL) and washed with water (2 X 30 mL) and brine (30 mL). The ethyl acetate layer was dried over anhydrous magnesium sulfate, filtered and the volatiles were removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, 3 : 1 ethyl acetate : hexane which provided an oil of the alcohol (615 mg, 90%). Anal. Calcd for $C_{24}H_{30}O_{10}$: C, 60.24; H, 6.31. Found: C, 60.09; H, 6.28.

To a solution of the alcohol (560 mg, 1.17 mmol) in anhydrous dichloromethane (15 mL) under an atmosphere of nitrogen at 0°C was added triethylamine (325 μL, 2.34 mmol) and methanesulfonyl chloride (100 μL, 1.29 mmol) dropwise over 10 minutes. The reaction mixture was allowed to warm to room temperature while stirring over 1 hour. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with distilled water (40 mL) and brine (25 mL). The ethyl acetate layer was dried over anhydrous $MgSO_4$, filtered and the volatiles were removed under reduced pressure.

To a solution of the crude mesylate obtained above in HPLC grade acetone (20 mL, Aldrich) was added sodium iodide

(523 mg, 3.51 mmol) under an atmosphere of nitrogen and the reaction mixture was allowed to stir for 2.5 hours at room temperature. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with distilled water (50 mL) and brine (30 mL). The ethyl acetate layer was dried over anhydrous $MgSO_4$, filtered and the volatiles were removed under reduced pressure.

To a suspension of sodium hydride (140 mg, 3.51 mmol, 60% in mineral oil) in freshly distilled anhydrous THF (5 mL) under an atmosphere of nitrogen at 0°C was added a solution of the alcohol (330 mg, 1.24 mmol) in freshly distilled anhydrous THF (20 mL) dropwise over 15 minutes. The reaction mixture was allowed to stir while warming to room temperature over 1.5 hours during which time the reaction became a nearly clear homogeneous solution. A solution of the above generated iodide in freshly distilled anhydrous THF (20 mL) was added dropwise over 20 minutes. The reaction mixture was allowed to stir for 3 hours at room temperature. The reaction mixture was recooled to 0°C and quenched with saturated NH_4Cl (10 mL). The reaction mixture was diluted with ethyl acetate (250 mL) and washed with distilled water (75 mL) and brine (25 mL). The ethyl acetate layer was dried over anhydrous $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 1% methanol / chloroform) to provide a white solid of the title compound (604 mg, 71%), mp 43-46°C. Anal. Calcd for $C_{38}H_{47}NO_{13}$ • 1.5 H_2O: C, 62.11; H, 6.58; N, 1.91. Found: C, 62.11; H, 6.48; N, 1.89.

To a suspension of silica gel (1.03 g) in dichloro methane (1.40 mL) was added 2.5% H_4SO_4 (103 mg). The reaction mixture was allowed to stir until the lower layer disappeared. The acetal (345 mg, 0.477 mmol) in dichloromethane (10 mL) was added and the reaction mixture was allowed to stir overnight. The reaction mixture was quenched with 1N NaOH (50 μL) and filtered. The volatiles were removed under reduced pressure to provide a crude mixture of the two aldehydes.

To a solution of the crude aldehydes in acetonitrile

(20 mL) under an atmosphere of nitrogen at 0°C was added N,N-diisopropylethylamine (166 µL), 0.954 mmol) followed by the dropwise addition of chloromethyl methyl ether (72 µL, 0.954 mmol) over 10 minutes. The reaction mixture was allowed to stir at room temperature for 48 hours during which time diisopropylethylamine (966 µL, 5.72 mmol) and chloromethyl methyl ether (432 mL, 5.72 mmol) were added in six portions. The reaction mixture was diluted with ethyl acetate (75 mL) and washed with distilled water (3 X 25 mL) and brine (1 X 25 mL). The ethyl acetate layer was dried over $MgSO_4$, filtered and the volatiles were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, 100 : 1 Chloroform : methanol) followed by radial chromatography (silica gel, 200 : 1 Chloroform : methanol) to provide an oil of the title compound (206 mg, 65%). Anal. Calcd for $C_{35}H_{41}NO_{14}$: C, 62.96; H, 6.19; N, 2.10. Found: C, 62.94; H, 6.24; N, 2.01.

Anti-1-[4-hydroxycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxybenzyloxy-2-(4-hydroxybenzamido)cyclopentane (COMPOUND 728)

To a solution of the aldehyde (142 mg, 0.213 mmol) in acetonitrile (50 ml) was added a solution of sulfamic acid (29 mg, 0.285 mmol) in distilled water (3 mL) dropwise over 5 minutes followed by the dropwise addition of a solution of $NaClO_2$ (32 mg, 0.285 mmol) in distilled water (3 mL) over 5 minutes. After allowing the reaction mixture to stir for 0.5 hours at room temperature the volatiles were removed under reduced pressure. The residue was dissolved in ethyl acetate (175 mL) and washed with distilled water 3 X 20 mL) and brine (1 X 20 mL). The ethyl acetate layer was dried over anhydrous $MgSO_4$, filtered, and the volatiles were removed under reduced pressure.

To a solution of crude carboxylic acid (90 mg, 0.132 mmol) in methanol (12 mL) was added conc. HCl (30 drops) at room temperature and the reaction mixture was allowed to stir for 5 hours. The volatiles were removed under reduced pressure. The product was chromatographed on a Dynamax©-60 C18

column (21 mm ID X 30 cm length) using a linear gradient from 100% A (0.1% TFA and 5% acetonitrile in water) to 100% B (pure acetonitrile) over 60 m at 15 mL / min. The product elutes in 23 minutes. Removal of the volatiles under reduced pressure provided the title compound as a white solid (60 mg, 88%), mp 161-164°C. Anal. Calcd for $C_{27}H_{25}NO_9 \cdot 0.5\ H_2O$: C, 62.79; H, 5.07; N, 2.71. Found: C, 62.58; H, 4.92; N, 2.66.

Certain of the compounds of the inventions were evaluated for likely pharmaceutical efficacy in inflammatory and other diseases by several methods. The first procedure measured the inhibition of PKC β_2 at 0.5 μm of the test compound. This procedure is described in Hannun, Y., Loomis, C., and Bell, R.M., *J. Biol. Chem.*, 1986, *261*:7184. The inhibition of PKC is probative of therapeutic efficacy in a wide range of disease states associated with PKC production or intermediation. The results are expressed as percent inhibition:

COMPOUND	PKCβ_2	COMPOUND	PKCβ_2
510	100	723	70
517	75	571	90
708	95	728	70
589	100	740	60
591	10	576	30
521	20	679	90
711	80	684	75
717	70	687	80
592	90	739	30
672	85	718	90
724	90	670	50
563	65	758	95
726	10	575	75

The second procedure measured the inhibition of MCF7 proliferation by tritiated thymidine incorporation assay. This protocol is described by Freshey, R.I., in *Culture of Animals Cells*, 1994, pp. 277-286, Wiley Liss, New York. Compounds 723,

521, and 591 were found to be strongly inhibitory while compounds 510, 517 and 708 were inhibitory to a lesser extent.

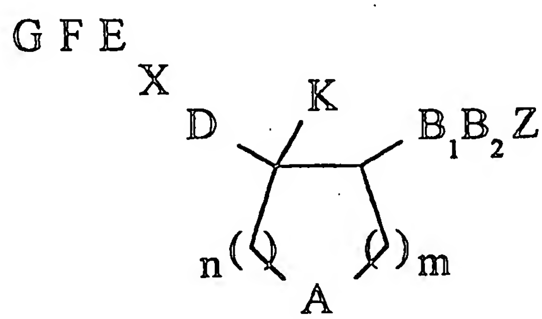
The third procedure measured the inhibition of superoxide release by neutrophils. This method is described in Trush, M.A., Wilson, M.E., and Van Dyke, K., *Methods in Enzymology*, **1978**, *107*:462 and Suzuki, Y., and Leher, R.J., *J. Clinical Investigation*, **1980**, *66*:1409. Superoxide release is associated with inflammatory pathways and its inhibition is probative of efficacy in a number of inflammatory diseases. Compounds 591, 521, 563, 575, 723, 740, and 759 showed strong inhibition of superoxide release.

The fourth procedure measured the inhibition of phorbol ester (TPA) induced inflammation in mouse ear. This is set forth in Carlson, R.P., Oneil-Davis, L., Chang, J., and Lewis, A.J., *Agents & Actions*, **1985**, *17*, 197. Compounds 510, 708, 589, 591, 717, 723, 728, 740, 679, 684, and 670 showed strong inhibition and 739 a somewhat lesser inhibition.

It will be appreciated that efficacy of the family of balanoids has been established through these tests. Persons skilled in the art will recognize that a test compound likely to have therapeutic activity may have activity in fewer than all of the assays. Accordingly, it is not necessary that a useful compound exhibit activity in each test. For example, compound 728 showed inactivity in the superoxide release assay, but was very active in the mouse ear test. Similarly, compound 670 showed low activity in the MCF7 proliferation assay, but showed good activity in the mouse ear test. Persons of skill in the art will be able to test particular compounds in accordance with the invention as a matter of routine to determine therepeutic activity.

What is claimed is:

1. A compound having the formula:



wherein:

A is CH_2, NR^1, O, S, or SO_2.

B_1 is NR^2, CH_2 or O;

B_2 is CO, CS or SO_2;

Z is phenyl, p-hydroxy phenyl, p-benzyloxy phenyl, p-benzoate phenyl, p-carboxy phenyl, 4-(2-hydroxyphenylcarbonyl)-3,5-dihydroxy phenyl, p-amino phenyl, 4-fluoro phenyl, 4-benzyloxy phenyl, p-methyl phenyl, p-benzyloxycarbonyl phenyl, p-nitro phenyl, 5-benzyloxy-2-indole, 5-hydroxy-2-indole, 3,4-dihydroxy phenyl, 2-benzyloxy phenyl, 2-hydroxy phenyl, phenyl, p-$NHSO_2CH_3$ phenyl, p-methoxymethyleneoxy phenyl, p-acetoxy phenyl;

D is NR^3, O or CH_2;

E is phenyl, 2-hydroxy benzene, 3-hydroxy benzene, 3-butyloxy benzene, 3-butyloxy-5-hydroxy benzene, 3-hexanoyloxy-5-hydroxy benzene, 3,5-dioctyloxy benzene, 3-octyloxy-5-hydroxy benzene, 3-methoxy-5-hydroxy benzene, 3,5-bis(acetoxy)benzene, 3-(methoxycarbonyl)oxy-5-hydroxy benzene, 3,5-dihydroxy phenyl, 3-ethoxy-5-hydroxy phenyl, 3,5-dibenzyloxy phenyl, 3,5-dimethoxy phenyl, 3-hydroxy-5-benzoate phenyl, phenyl, 3,5-dimethoxymethyleneoxy phenyl, 3-methoxycarbonyloxy phenyl, 3-acetoxy-5-hydroxy phenyl;

F is CO or CH_2;

G is phenyl, 2-carboxy-6-hydroxy phenyl, 2-ethoxycarbonyl-6-hydroxy phenyl, 2-hydroxy phenyl, 2-benzyloxycarbonyl phenyl, 2-hydroxy naphthyl, 2,3,5,6,-tetramethyl phenyl, 2,6-dihydroxy phenyl, 2,6-dimethoxy phenyl, 2-carboxy cyclohexane, 2-hydroxy cyclohexane, 2-hydroxy-1-naphthyl, 2,6-dichloro phenyl, 2-methoxy-6-hydroxy phenyl, 2-carboxy-3-pyridine, 3-carboxy-2-pyridine, phenyl, 3,4-dibenzyloxyphenylcarbonyl phenyl, 3,4-dihydroxy phenyl, 2-methoxycarbonyl-6-hydroxy phenyl, 2-butoxycarbonyl-6-hydroxy phenyl, 2-(2-methylpropyloxycarbonyl)-6-hydroxy phenyl, 2-nitrilo-6-hydroxy phenyl, 2-carboxy phenyl, 2-(4-acetoxy-benzyloxycarbonyl)-6-hydroxy phenyl, 2-benzyloxycarbonyl -6-benzyloxy phenyl, 2,6-dibenzyloxy phenyl, 2-benzyloxycarbonyl cyclohexane, 1-benzyloxy-2-naphthyl, 2-methoxy-6-benzyloxy phenyl, 2-benzyloxycarbonyl-3-pyridinyl, 3-benzyloxycarbonyl-2-pyridinyl, 2-benzyloxyphenyl, 2-nitrilo-6-benzyloxy phenyl, 3,4-dibenzyloxy phenyl, 2-benzyloxy-1-naphthyl, 6-benzyloxy-2-tetrazolyl phenyl, 6-hydroxy-2-tetrazolyl phenyl, 2-(2-methyltetrazolyl)-6-hydroxyphenyl, 2-(3-methyltetrazolyl)-6-hydroxyphenyl, 2-hydroxy-1-(5,6,7,8-tetrahydro) naphthyl, 3-benzyloxycarbonyl-4-benzyloxy phenyl, 3-carboxy-4-hydroxy phenyl, 2-methoxymethyleneoxy phenyl, 2-ethoxycarbonyl-6-benzyloxy phenyl, 2-benzyloxy carbonyl-1-naphthyl, 2-carboxy-1-naphthyl, 2-benzyloxy-6-methyl phenyl, 2-methyl-6-hydroxy phenyl, 2-acetoxy-6-ethoxycarbonyl phenyl, 2-(cyclohexylmethoxycarbonyl)-6-hydroxy phenyl, 2-carboxy-6-benzyloxy phenyl, 2-methoxycarbonyl-6-benzyloxy phenyl, 2-hexanoyloxy-6-carboxy phenyl;

X is CO;

K is H or lower alkyl;

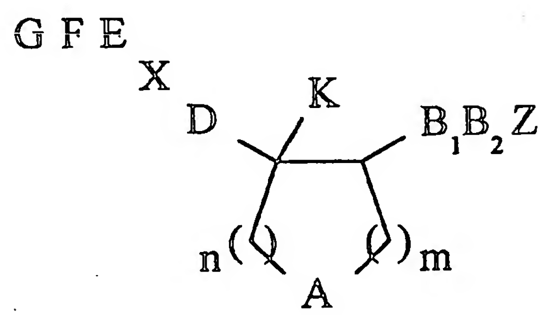
R^1, R^2, or R^3 are, independently hydrogen, lower alkyl or aryl;

m is 1; and

n is 3; or, a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1 wherein:
A is NH or CH_2;
B1 is NH;
B2 is CO;
Z is p-hydroxyphenyl;
D is O;
E is 3,5-dihydroxy benzene;
F is CO;
X is CO;
m is 1; and
n is 3.

3. A compound having the formula:



wherein:

A is: CH_2, NR^1, S, SO_2, or O;

B1 is: NR^2, O or CH_2;

B2 is: CO, CS, or SO_2;

Z is: R^4, aryl, heteroaryl, substituted aryl or substituted heteroaryl;

D is: NR^3, O or CH_2;

E is: R^5, aryl, heteroaryl, substituted aryl or substituted heteroaryl;

F is: CO, CS, $CH(OR^6)$, CH_2, O, S or NR^6;

G is: R^7, aryl, heteroaryl, substituted aryl, substituted cycloalkyl, or substituted heteroaryl;

K is H or lower alkyl;

X is: CO, CS, CH_2, CNR^8 or CCR^9R^{10};

R^1, R^2, R^3, R^4, R^6, R^7, R^8, R^9 and R^{10} are, independently, hydrogen, lower alkyl, aryl or JR^{11};

R^5 is: lower alkyl or aryl;

J is: CO, C=NH, C=N-lower alkyl, or SO_2;

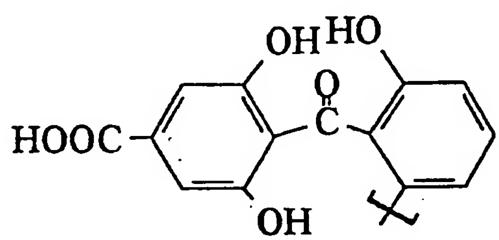
R^{11} is: lower alkyl, aryl, alkamino, arylamino, aryloxy, or alkoxy;

m is: 1-4;

n is: 1-4; and

m plus n is up to 5;

providing that if m is 3, A is NH, B1 is O, B2 is CO, Z is p-hydroxyphenyl, D is NH, X is CO, and E, F, and G, taken together, are



then n is not 1, or a pharmaceutically acceptable salt thereof.

4. A compound according to Claim 3 wherein B1 is NH.

5. A compound according to Claim 3 wherein B2 is CO.

6. A compound according to Claim 3 wherein Z is: hydroxy substituted aryl, ether substituted aryl, halo substituted aryl, hydroxy substituted heteroaryl, halo substituted hereroaryl, or ether substituted heteroaryl.

7. A compound according to Claim 3 wherein Z is p-hydroxyphenyl, p-fluorophenyl, or 5-hydroxy indole.

8. A compound according to Claim 3 wherein D is O.

9. A compound according to Claim 3 wherein E is: hydroxy substituted aryl, ether substituted aryl, acyloxy substituted aryl, or hydroxy substituted heteroaryl.

10. A compound according to Claim 3 wherein E is 3,5-dihydroxyphenyl, 3,5-di-lower alkoxyphenyl, 3-hydroxyphenyl, 3,5-diacyloxy phenyl, or 3-acyloxy-5-hydroxyphenyl.

11. A compound according to Claim 3 wherein F is CO.

12. A compound according to Claim 3 wherein G is: hydroxy substituted aryl, ether substituted aryl, carboxyl substituted aryl, tetrazole substituted aryl, cyano substituted aryl, alkoxycarbonyl substituted aryl, acyloxy substituted aryl, hydroxy substituted heteroaryl, ether substituted heteroaryl, carboxyl substituted heteroaryl or combinations of such substitutions.

13. A compound according to Claim 3 wherein G is phenyl, 2-hydroxy phenyl, 2,6-dihydroxy phenyl, 2-lower alkoxy phenyl, 2,6-di-lower alkoxy phenyl, benzene 2-carboxylic acid, 6-hydroxybenzene- 2-carboxylic acid, 2-acyloxy benzene-2-carboxylic acid, 2-hydroxy-6-(2-tetrazoyl)-benzene, 2-hydroxy-6-lower alkoxycarbonyl benzene, 2-acyloxy-6-lower alkoxy carbonyl benzene, 2-hydroxy-6-(trifluoromethylsulfonylamino)-benzene, 2-cyano-6-hydroxybenzene, and 2-hydroxy-5,6,7,8-tetrahydronaphth-1-yl.

14. A compound according to Claim 3 wherein X is CO.

15. A compound according to Claim 3 where m is 1 or 2.

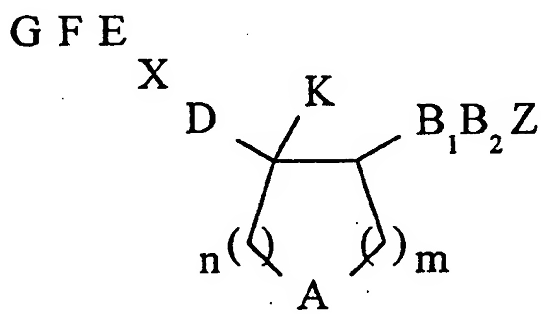
16. A compound according to Claim 3 where n is 1, 2 or 3.

17. A compound according to Claim 3 where n is 1 and m is 1.

18. A compound according to Claim 3 where n is 1 and m is 3.

19. A method of inhibiting protein kinase C comprising contacting protein kinase C with an effective amount of a compound in accordance with claim 1 or 3.

20. A method of inhibiting protein kinase C comprising contacting protein kinase C with an effective amount of a compound having the formula:



wherein:

A is CH_2, NR^1, S, SO_2, or O;

B1 is NR^2, O or CH_2;

B2 is CO, CS, or SO_2;

Z is R^4, aryl, heteroaryl, substituted aryl or substituted heteroaryl;

D is NR^3, O or CH_2;

E is R^5, aryl, heteroaryl, substituted aryl or substituted heteroaryl;

F is CO, CS, $CH(OR^6)$, CH_2, O, S or NR^6;

G is R^7, aryl, heteroaryl, substituted aryl or substituted heteroaryl;

K is H or lower alkyl;

X is CO, CS, CH_2, CNR^8 or CCR^9R^{10};

R^1 is hydrogen, lower alkyl, aryl or JR^{11};

J is CO, C=NH or SO_2;

R^{11} is lower alkyl, aryl, alkylamino or alkoxy;

R^2, R^3, R^4, R^6, R^7, R^8, R^9 and R^{10} are, independently hydrogen, lower alkyl or aryl;

R^5 is lower alkyl or aryl;

R^{11} is: lower alkyl, aryl, alkamino, arylamino, aryloxy, or alkoxy;

m is 1-4; and

n is 1-4;

wherein m plus n is less than or equal to 5; or, a pharmaceutically acceptable salt thereof.

21. The method according to Claim 20 wherein:

A is NH, CH_2 or NR^1.

B1 is NR^2 or O;

B2 is CO or CS;

Z is phenyl or hydroxy benzene;

D is NR^3, O or CH_2;

E is 3,5-hydroxy benzene or 3,5-methoxy benzene;

F is CO or CH_2;

G is phenyl, 2-hydroxy phenyl, 2,6-dihydroxy phenyl, 2-lower alkoxy phenyl, 2,6-di-lower alkoxy phenyl, benzene 2-carboxylic acid, 6-hydroxybenzene- 2-carboxylic acid, 2-acyloxy benzene-2-carboxylic acid, 2-hydroxy-6-(2-tetrazoyl)-benzene, 2-hydroxy-6-lower alkoxycarbonyl benzene, 2-acyloxy-6-lower alkoxy carbonyl benzene, 2-hydroxy-6-(trifluoromethylsulfonyl amino)-benzene, 2-cyano-6-hydroxybenzene, and 2-hydroxy-5,6,7,8-tetrahydronaphth-1-yl.

X is CO;

R^1, R^2, or R^3 are, independently hydrogen, lower alkyl or aryl;

m is 1; and

n is 3;

or, a pharmaceutically acceptable salt thereof.

22. The method according to Claim 20 wherein:

A is NH or CH_2;

B1 is NH;

B2 is CO;

Z is p-hydroxyphenyl;

D is O;

E is 3,5-hydroxy benzene;

F is CO;

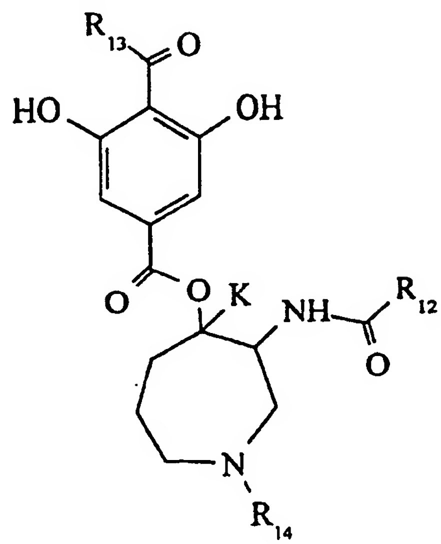
G is phenyl, 2-hydroxy phenyl, 2,6-dihydroxy phenyl, 2-lower alkoxy phenyl, 2,6-di-lower alkoxy phenyl, benzene 2-carboxylic acid, 6-hydroxybenzene- 2-carboxylic acid, 2-acyloxy benzene-2-carboxylic acid, 2-hydroxy-6-(2-tetrazoyl)-benzene, 2-hydroxy-6-lower alkoxycarbonyl benzene, 2-acyloxy-6-lower alkoxy carbonyl benzene, 2-hydroxy-6-(trifluoromethylsulfonyl amino)-benzene, 2-cyano-6-hydroxybenzene, and 2-hydroxy-5,6,7,8-tetrahydronaphth-1-yl.

X is CO;

m is 1; and

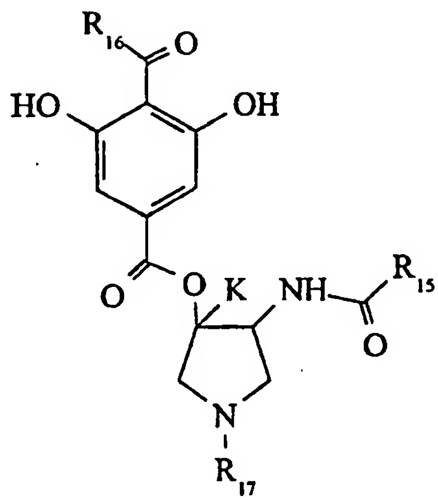
n is 3.

23. A compound having the formula:



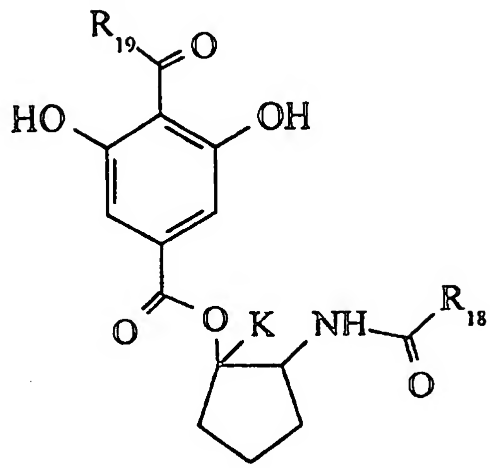
Wherein R_{12} is 4-hydroxyphenyl, 4-lower alkoxyphenyl, 4-fluorophenyl, 5-hydroxy-2-indolyl, and 4-acetoxyphenyl; R_{13} is 2-carboxy-6-hydroxyphenyl, 2,6-dihydroxyphenyl, 2,6-di-lower alkoxyphenyl, 2-carboxy-6-lower alkoxyphenyl, 2-hydroxy-5,6,7,8-tetrahydronaphthyl, 2-methoxycarbonyl-6-hydroxyphenyl, 2-ethoxycarbonyl-6-hydroxy phenyl, 2-lower alkoxycarbonyl-6-hydroxyphenyl, 2-butoxycarbonyl-6-hydroxyphenyl, 2-ethoxycarbonyl-6-acetoxyphenyl, 2-hydroxy-1-naphthyl, $COCH_2OCOC(CH_3)_3$, 2-tetrazolyl-6-hydroxyphenyl; and R_{14} is H, methylsulfonyl, lower alkylsulfonyl, beta naphthylsulfonyl, 4-toluene sulfonyl, tert-butoxy carbonyl, lower alkoxy carbonyl, $(CH_3CH_2O)_2PO$-, methyl, ethyl, propyl, isopropyl, lower alkyl, tert-butylimino; K is H or lower alkyl; and salts thereof.

24. A compound having the formula:



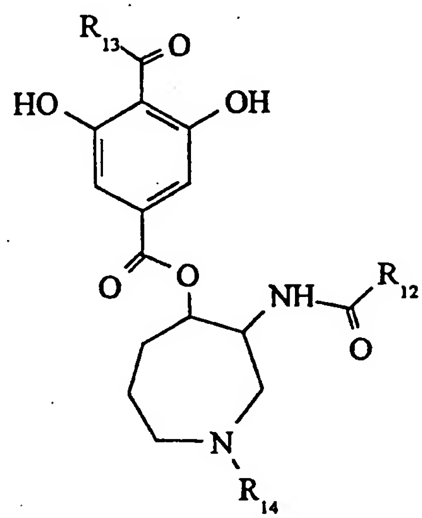
wherein R_{15} is 4-hydroxyphenyl, 4-lower alkoxyphenyl, 4-fluorophenyl, 5-hydroxy-2-indolyl, and 4-acetoxyphenyl; R_{16} is 2-carboxy-6-hydroxyphenyl, 2,6-dihydroxyphenyl, 2,6-di-lower alkoxyphenyl, 2-carboxy-6-lower alkoxyphenyl, 2-hydroxy-5,6,7,8-tetrahydronaphthyl,2-methoxycarbonyl-6-hydroxyphenyl, 2-ethoxycarbonyl-6-hydroxy phenyl, 2-lower alkoxycarbonyl-6-hydroxyphenyl, 2-butoxycarbonyl-6-hydroxyphenyl, 2-ethoxycarbonyl-6-acetoxyphenyl, 2-hydroxy-1-naphthyl, $COCH_2OCOC(CH_3)_3$, 2-tetrazolyl-6-hydroxyphenyl; and R_{17} is H, methylsulfonyl, lower alkylsulfonyl, beta naphthylsulfonyl, 4-toluene sulfonyl, tert-butoxy carbonyl, lower alkoxy carbonyl, $(CH_3CH_2O)_2PO$-, methyl, ethyl, propyl, isopropyl, lower alkyl, tert-butylimino, K is H or lower alkyl; and salts thereof.

25. A compound having the formula:



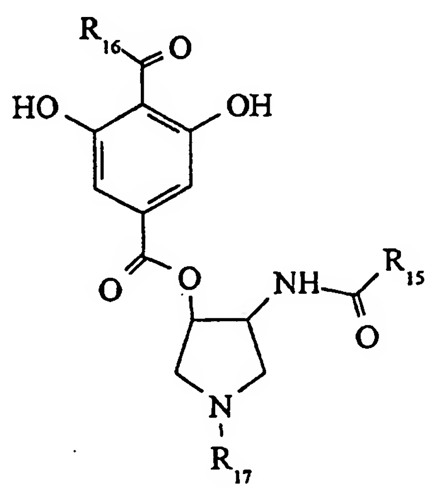
wherein R_{18} is 4-hydroxyphenyl, 4-lower alkoxyphenyl, 4-fluorophenyl, 5-hydroxy-2-indolyl, and 4-acetoxyphenyl; and R_{19} is 2-carboxy-6-hydroxyphenyl, 2,6-dihydroxyphenyl, 2,6-dicarboxyphenyl, 2,6-di-lower alkoxyphenyl, 2-carboxy-6-lower alkoxyphenyl, 2-hydroxy-5,6,7,8-tetrahydronaphthyl, 2-methoxycarbonyl-6-hydroxyphenyl, 2-ethoxycarbonyl-6-hydroxyphenyl, 2-lower alkoxycarbonyl-6-hydroxyphenyl, 2,6-dilower alkoxycarbonylphenyl, 2-butoxycarbonyl-6-hydroxyphenyl, 2-ethoxycarbonyl-6-acetoxyphenyl, 2-hydroxy-1-naphthyl, $COCH_2CH_2OCOC(CH_3)_3$, 2-tetrazolyl-6-hydroxyphenyl; K is H or lower alkyl; and salts thereof.

26. A compound having the formula:



Wherein R_{12} is 4-hydroxyphenyl, 4-fluorophenyl, 5-hydroxy-2-indolyl; R_{13} is 2-carboxy-6-hydroxyphenyl, 2,6-dihydroxyphenyl; and R_{14} is H, methylsulfonyl, beta naphthylsulfonyl, 4-toluene sulfonyl, tert-butoxy carbonyl; and salts thereof.

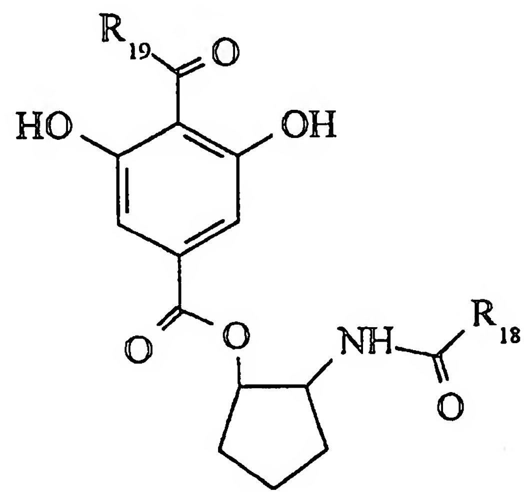
27. A compound having the formula:



wherein R_{15} is 4-hydroxyphenyl, 4-acetoxyphenyl; R_{16} is 2-carboxy-6-hydroxyphenyl,2-hydroxy-5,6,7,8-tetrahydronaphthyl, 2-methoxycarbonyl-6-hydroxyphenyl, 2-butoxycarbonyl-6-hydroxyphenyl, 2-ethoxycarbonyl-6-acetoxyphenyl, 2-hydroxy-1-

naphthyl; and R_{17} is H, $(CH_3CH_2O)_2PO-$, isopropyl, tert-butylidinyl, and salts thereof.

28. A compound having the formula:



wherein R_{18} is 4-hydroxyphenyl; and R_{19} is $COCH_2OCOC(CH_3)_3$, 2-tetrazolyl-6-hydroxyphenyl, 2-carboxy-6-hydroxyphenyl, 2-methoxycarbonyl-6-hydroxyphenyl; and salts thereof.

29. A compound in accordance with claim 24, 25, 26, 27, 28, or 29 in a pharmaceutically acceptable carrier or diluent.

30. A method of inhibiting protein kinase C comprising contacting protein kinase C with an effective amount of a compound in accordance with claim 24, 25, 26, 27, 28, or 29.

31. A method of treating an inflammatory disease comprising administering to a mammal suspected of having an inflammatory disease an effective amount of a compound in accordance with claim 24, 25, 26, 27, 28, or 29.

32. (-)-Trans-4-(4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxy benzoyloxy)-3-(4-hydroxybenzamido)azepine Trifluoroacetic Acid Salt, (-)-Balanol; *syn*-4-[4-(2-hydroxycarbonyl-6-hydroxy benzoyl)-3,5-dihydroxy benzoyloxy]-3-

(4-hydroxybenzamido) perhydroazepine trifluoroacetic acid salt; trans-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-hydroxycarbonyl benzoyl)-3,5-dihydroxybenzoyloxyl]pyrrolidinium trifluoro acetate; trans-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-naphth-1-oyl)-3,5-dihydroxybenzyoyloxyl]pyrrolidine trifluoroacetic acid salt; (+)-*Anti*-4-[3,5-dihydroxy-4-(2,6-dihydroxy benzoyl)] hexahydro-3-(4-hydroxybenzoylamine)azepine; 1-Isopropyl-trans-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-hydroxycarbonyl benzoyl)-3,5-dihydroxybenzoyloxyl]pyrrolidinium trifluoro acetate; *anti*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-1-[5,6,7,8-tetrahydro-naphthoyl])-3,5-dihydroxy benzyoyl oxy]pyrrolidine trifluoroacetic acid salt; *anti*-1-[4-(2-Hydroxycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-2-(4-hydroxybenzamido) cyclopentane; (±)-*trans*-3-(4-hydroxy benzamido)-4-[4-(2-hydroxy-6-methoxycarbonyl benzoyl)-3,5-dihydroxybenzoyloxy]pyrrolidinium hydrochloride; racemic tosyl-balanol;*trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-hydroxycarbonylbenzoyl)-3,5-dihydroxybenzamido] pyrrolidine trifluoroacetic acid salt; (±)-*trans*-3-(4-acetoxy benzamido)-4[4-(2-acetoxy-6-ethoxycarbonylbenzoyl)-3-acetoxy-5-hydroxy benzoyloxy] pyrrolidinium trifluoroacetate; *(±)anti*-1-[4-(2-Methoxycarbonyl-6-hydroxybenzoyl)-3,5-dihydroxybenzoyloxy]-2-(4-hydroxybenzamido)-cyclopentane; (±)-*trans*-4-[4-(2-hydroxy carbonyl-6-hydroxybenzoyl)-3,5-dihydroxy benzoyloxy]-3-(4-hydroxybenzamido)-1-(2-naphthalene sulfonyl) azepine; (±)-1-1-methylethyl-*trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-methoxycarbonylbenzoyl)-3,5-dihydroxybenzoyl oxy]pyrrolidine trifluoroacetic acid salt; *trans*-3-(4-hydroxybenzamido)-4-[4-(2-hydroxy-6-butoxycarbonylbenzoyl)-3,5-dihyrdroxybenzoyloxy] pyrrolidine trifluoroacetic acid salt; (+)-*trans*-3-(4-Hydroxy benzamido)-4-[3,5-dihydroxy-4-(2- carboxy-6-hydroxybenzoyl benzoyloxy]-N-diethylphosphonato pyrrolidine; (±)-*trans*-2-[4-(6-hydroxy-2-tetrazolylbenzoyl)-3,5-dihydroxybenzoyloxy]-1-(4-hydroxybenzamido)cyclopentane; (±)-*trans*-3-(4-hydroxybenzamido) -4-[4-(2-hydroxy-6-methoxycarbonylbenzoyl)-3,5-dihydroxy benzamido] pyrrolidine trifluoroacetic acid salt; mesyl-balanol; 1-[4-(2-carboxy-6-hydroxybenzoyl)-3,5-dihydroxy

benzyloxy]-2-(4-hydroxybenzamido) cyclopentane; (+)-*trans*-3-(4-Fluorobenzamido)-4-[4-(2-carboxy-6-hydroxy) benzoyl-3,5-dihydroxy]benzoyloxyhexahydroazepine trifluoroacetic acid salt; (±)-*anti*-3-[4-(2-Carboxy-6-hydroxybenzoyl)-3,5-dihydroxy benzoyl-oxyl-1-[N(1,1-dimethyl ethyl)iminomethyl]-4-(4-hydroxybenzamido)-pyrrolidine, trifluoroacetic acid salt; BOC-Balanol; (+)-*trans*-4-[4-(2-carboxy-6-hydroxy)benzoyl-3,5-dihydroxy]benzoyloxy-3-[2-(5-hydroxyindolyl)formamido]-hexahydroazepine trifluoroacetic acid salt; or (±)-*trans*-2-[3,5-Dihydroxy-4-(2-hydroxy-6-(trifluoro methane-sulfonylamino) benzoyl)benzoyloxy]-1-(4-hydroxy benzamido)-cyclopentane Hemihydrate; or a salt or pharmaceutically acceptable solution, suspension, or dispersion thereof.

33. 3-Benzyloxy-2-[2,6-dibenzyloxy-4-(1,1-dimethylethoxy carbonyl)benzoyl]benzoic acid or a lower alkyl ester thereof.

34. 3,5-dimethoxymethyleneoxy-4-[2-methoxymethyleneoxy-6-(1,6-dioxanyl)]benzoylbenzoic acid or a lower alkyl ester thereof.